The Interplay between Type Two Diabetes Mellitus and Prostate

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The Interplay between Type Two Diabetes Mellitus and Prostate Cancer

Thesis presented in accordance with the requirements for the

Degree of Doctor of Philosophy

by

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Acknowledgement

I first started working in what was then the Cancer Epidemiology Group, as an academic clinical fellow in 2012. I was meant to stay for a 3 month project and 5 years later I am still here and very proud to be completing my PhD in the department, which is now the TOUR group. I would like to thank James Spicer, my academic supervisor at that time, and Simon Chowdhury, my clinical supervisor, for the introduction to Professor Holmberg and Dr Mieke Van Hemelrijck.

After completing that initial project, a meta-analysis looking at glucose and risk of cancer, my interest in epidemiology was rekindled, having previously spent 4 months working in the epidemiology unit at Imperial College. With a huge amount of help, encouragement and enthusiasm from Mieke, we were able to put together a proposal and gain funding for my PhD thesis. Following an interlude for my maternity leave I was delighted to be able to join the department in October 2015 and begin work on this thesis. Mieke has from that first meeting been a most inspiring and supportive first supervisor, with her never tiring work ethic and dynamism, I could have never completed this thesis without her support.

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Abstract

Aims/Objectives: This thesis aims to explore the interplay between type two diabetes mellitus (T2DM) and prostate cancer (PCa) with regards to treatments of both conditions and disease outcomes.

Background: PCa and T2DM are both increasingly prevalent conditions, meaning that they often occur together. However, the relationship between the two is complex.

Plan of investigation/Methods: To investigate the complex interplay between the two, the thesis was divided into the following projects:

(1) Using data from Prostate Cancer data Base Sweden (PCBaSe) Sweden this thesis investigated:

i) the impact of co-existing T2DM on receiving curative treatment for PCa

ii) the impact of a PCa diagnosis on T2DM treatment

iii) how the type and duration of androgen deprivation therapy (ADT) may affect risk of getting T2DM

(2) Evaluation of whether presence of T2DM and other components of the metabolic syndrome (MetS) affects response to ADT using data from patients enrolled in the STAMPEDE trial

(3) Assessment of which tumour components are affected by metformin through a randomised controlled trial, METAL (Metformin And Longevity).

Results: Men with T2DM were 20% less likely to receive curative treatment for intermediate and high risk PCa compared to those without T2DM after adjusting for age, co-morbidity and tumour characteristics. Moreover, men with pre-existing T2DM were at increased risk of needing treatment escalations following a PCa diagnosis, particularly those treated with ADT. An increased risk of T2DM following treatment with ADT was also shown in which the duration and type of ADT received was important. Finally, baseline metabolic aberrations, including T2DM, in men commencing ADT for advanced PCa increased the risk of local and metastatic progression.

Conclusion: This thesis highlights the complexity of the interplay between T2DM and PCa, in which both conditions impact on both the treatment and disease outcomes of the other.

Table of Contents

List of Tables

List of Figures

List of Abbreviations

95% CI	95% confidence interval
ADT	Androgen deprivation therapy
AMPK	5'-AMP- activated protein kinase
AS	Active surveillance
ATP	Adenosine triphosphate
BCR	Biochemical recurrence
BMI	Body mass index
CCI	Charlson Comorbidity Index
CMOP	Centre for Molecular Oncologic Pathology
CRA	Clinical research associate
CRP	C-reactive protein
CRPC	Castrate resistant metastatic prostate cancer
CTIMP	Clinical trial of investigational medicinal product
CVD	Cardiovascular disease
DFCI	Dana Farber Cancer Institute
DM	Diabetes mellitus
DPP-4	Dipeptidyl peptidase-4
DRE	Digital rectal examination
EBRT	External beam radiotherapy
ECOG	Eastern Cooperative Oncology Group
EPIC	European Prospective Investigation into Cancer and Nutrition
ERK	Extracellular signal–regulated kinases
ESMO	European Society of Medical Oncology

FASN	Fatty acid synthase
FBG	Fasting blood glucose
FDA	Food and Drug Administration
FFS	Failure free survival
GLP-1	Glucagon-like peptide-1
GnRH	Gonadotrophin releasing hormone
GWAS	Genome-wide association studies
H&E	Hematoxylin and eosin
HbA1c	Glycosylated haemoglobin
HDL	High density lipoprotein
HR	Hazard ratio
ICD	International Classification of Diseases
IDF	International Diabetes Federation
IGF-1	Insulin like growth factor-1
IL-6	Interleukin (IL)-6
IMP	Investigational medicinal product
INCA	Information Network for Cancer care
LDL	Low density lipoproteins
LFT	Liver function tests
LISA	Longitudinal database on socioeconomic factors
METAL	Metformin and longevity
MetS	Metabolic syndrome
MHRA	Medicines and Healthcare products Regulatory Agency
MICE	Multiple imputation using chained equations

MRI	Magnetic resonance imaging
MTOR	Mammalian target of rapamycin
NDR	National diabetes register
NF-KB	Nuclear factor kappa-B
NHANES	National Health and Nutrition Examination Survey
NPCR	National prostate cancer register of Sweden
OHA	Oral hypoglycaemics
OR	Odds ratio
OS	Overall survival
PAI-1	Plasminogen activator inhibitor
PCa	Prostate Cancer
PCBaSe	Prostate Cancer data Base Sweden
PCSD	Prostate cancer-specific death
PET-CT	Positron emission tomography-computerized tomography
PET-MRI	Positron emission tomography–magnetic resonance imaging
PPARs	Peroxisome proliferator-activated receptors
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analysis
PSA	Prostate specific antigen
R&D	Research and development
RCT	Randomised Controlled Trial
REC	Research Ethics Committee
RP	Radical prostatectomy
RR	Relative risk

SEER	Surveillance, epidemiology and end results program
SDR	Standardised death rate
SMPC	Summary of Product Characteristics
SMR	Standardised mortality rate
SNPs	Single nucleotide polymorphisms
SOP	Standard operating procedure
STAMPEDE	Systemic Therapy for Advancing or Metastatic Prostate Cancer: Evaluation of Drug Efficacy
STROBE	Strengthening the reporting of observational studies in epidemiology
SU	Sulphonylurea
T2DM	Type two diabetes mellitus
TGs	Triglycerides
TUNEL	Terminal deoxynucleotidyl transferase dUTP nick end labelling
WW	Watchful waiting

Chapter I- Introduction and Research Objectives

Prostate cancer (PCa) is the most common cancer in men, with over 40,000 men diagnosed each year in the UK (1). There are also 3.2 million people in the UK who have been diagnosed with Type Two Diabetes (T2DM) and it is estimated that this will rise to 5 million by 2025 (2). It is therefore clear that both PCa and T2DM are prevalent conditions, meaning that they often occur together in the same individual. However, the relationship between the two is much more complex than two prevalent conditions which just concurrently occur in men. This thesis explores the complex interplay between T2DM and PCa with regards to treatments of both conditions and disease outcomes.

More specifically, this thesis is divided into the following chapters:

Before explaining the different research projects enclosed in this thesis, Chapter II covers the relevant background to this thesis and describes the biology, descriptive epidemiology, risk factors, clinical management and treatment of PCa, T2DM and MetS. Next, Chapter III systematically reviews the existing literature exploring the interplay between T2DM and PCa. It specifically covers the impact of pre-existing T2DM on PCa incidence, the impact of pre-existing T2DM on PCa grade and stage, the impact of pre-existing T2DM on PCa outcomes and mortality, and the interaction between T2DM and PCa treatments.

Chapter IV uses data from Prostate Cancer data Base Sweden (PCBaSe) Sweden and reports on:

i) The impact of co-existing T2DM on receiving curative treatment for PCa

ii) The impact of a PCa diagnosis on T2DM treatment

iii) How the type and duration of androgen deprivation therapy (ADT) may affect the risk of getting T2DM

Chapter V evaluates whether presence of T2DM and other components of the metabolic syndrome (MetS) affect response to ADT in advanced PCa using data from patients enrolled in the Systemic Therapy for Advancing or Metastatic Prostate Cancer: Evaluation of Drug Efficacy (STAMPEDE) trial.

Chapter VI assesses which tumour components are affected by metformin through designing, setting up and running a randomised controlled trial investigating the

biological effects of metformin in localised PCa – METAL (Metformin And Longevity) trial.

Finally, Chapter VII summarises the overall findings of this thesis before discussing future directions of research.

Chapter II – Background

This chapter will describe the biology, descriptive epidemiology, risk factors, clinical management and treatment of PCa, T2DM and MetS, where appropriate.

Prostate cancer biology

The normal prostate

The prostate gland is a large accessory gland of the male reproductive system. It has important functions in the production of spermatozoa including the secretion of enzymes which are necessary for their normal functioning (3). It is a walnut shaped gland of approximately 4cm in health (4). Anatomically it sits between the penis and the bladder surrounding the neck of the bladder and pre-prostatic portion of the urethra (5) (**Figure 1**). The gland consists of anterior, median, right and left lateral and posterior lobes. It can also be divided into several zones. The central zone surrounds the ejaculatory duct, whilst the peripheral zone provides the bulk of the gland. There is also a transitional zone which surrounds the prostatic urethra (4) (**Figure 2**).

Histologically there are two distinct areas within the prostate: the glandular epithelium and the stromal compartment. Within the glandular epithelium there are luminal and basal cells, with occasional neuroendocrine cells. The stromal compartment contributes at least half of the volume of the gland and is formed of a fibromuscular layer called the pseudocapsule (4).

Figure 1: Sagittal view of the prostate and surrounding structures (4)

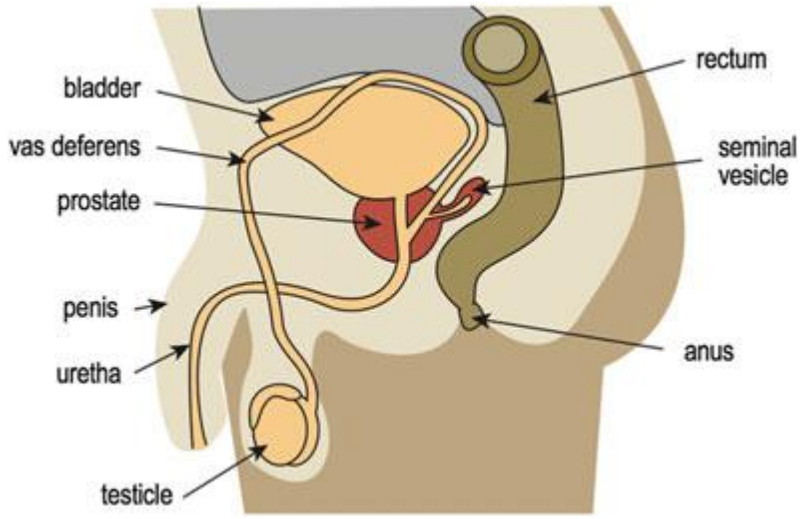
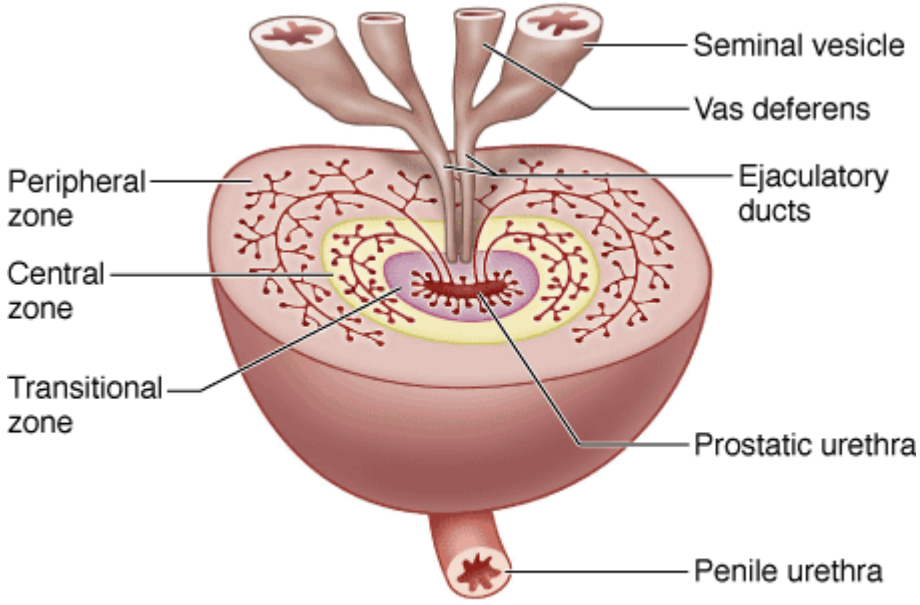


Figure 2: The zones of the prostate gland



Source: Mescher AL: *Junqueira's Basic Histology: Text and Atlas, 12th Edition:* http://www.accessmedicine.com

Prostate cancer histopathology

Adenocarcinoma accounts for 95% of PCa and its diagnosis is based on a constellation of architectural and cytological appearances, though it can be difficult to make the diagnosis because the appearances are subtle (6). Adenocarcinoma arises from the glandular epithelial cells and can be seen as small infiltrating glands with prominent nuclei. These tumour cells have darker purple cytoplasm on hematoxylin and eosin (H&E) stained sections than benign cells. Other cytological features of malignant glands include intraluminal crystalloids and blue-tinged mucin. The remaining 5% of PCa include neuroendocrine and urothelial (transitional cell) carcinomas, which are not discussed here as they are beyond the scope of this thesis.

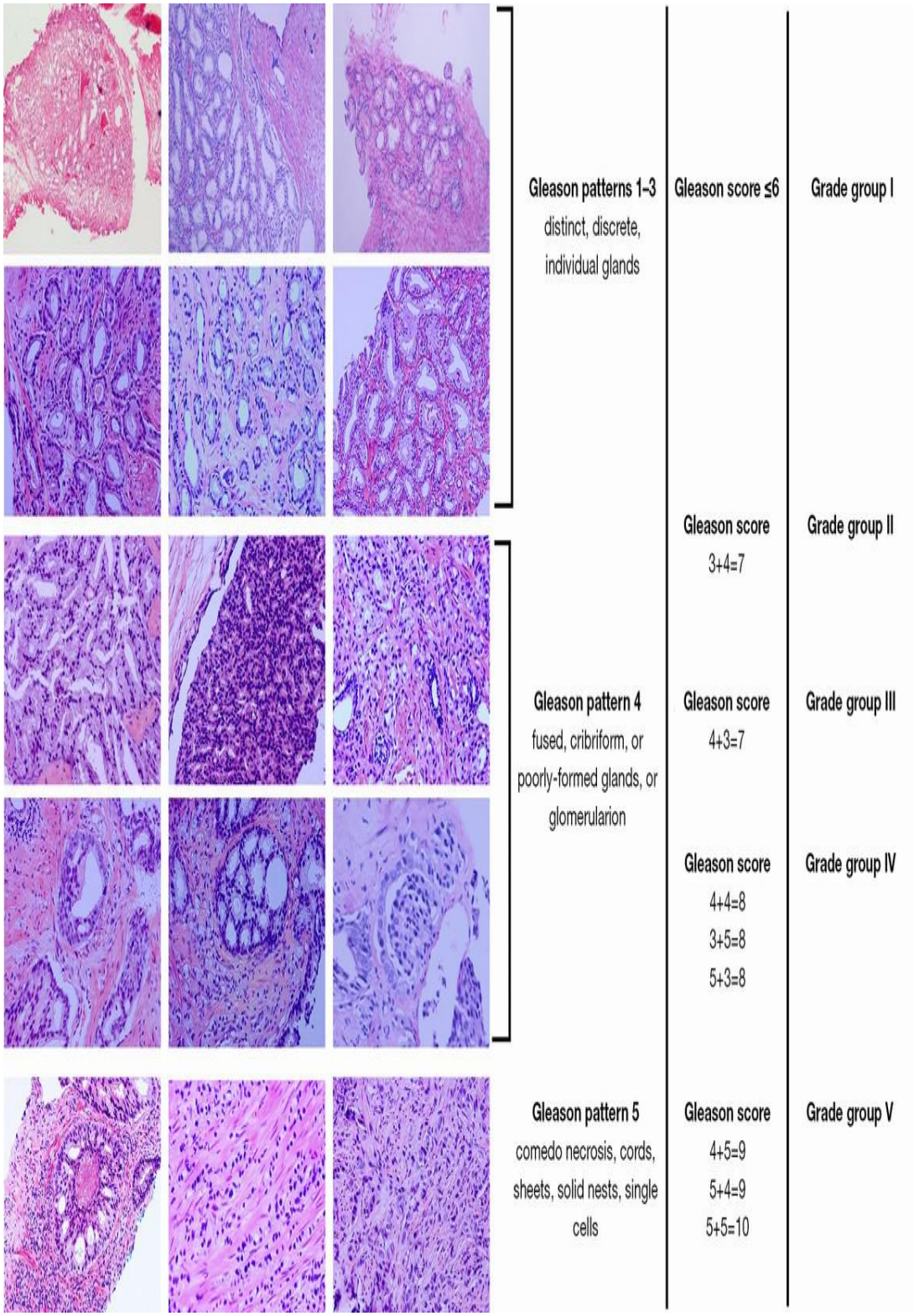
The Gleason Grading system was devised by Donald Gleason in 1996 and is based upon the architectural appearance of the PCa. Both the primary pattern and second most common pattern are identified and are given a score of 1-5. These are then added together to give a Gleason Sum Score. In practice grade 1 and 2 are not used, so most grading begins at 3 (**Figure 3**). This grading system has been universally adopted and remains the most useful tissue based prognostic tool in PCa (4).

More recently a Gleason Grade Group system has been developed consisting of 5 groups (**Figure 3**):

Grade group 1: Gleason score ≤6
Grade group 2: Gleason score 3+4 = 7
Grade group 3: Gleason score 4+3 = 7
Grade group 4: Gleason score = 8
Grade group 5: Gleason scores = 9-10

The grade group system was validated in an analysis of over 20,000 patients undergoing radical prostatectomy. There was an increasing risk of biochemical recurrence (BCR) and prostate cancer mortality with increasing grade (7) . In 2014 this new Gleason Grade Group was accepted at the International Society of Urological Pathology Consensus Conference on Gleason Grading of Prostatic Carcinoma (8).

Figure 3: The evolving Gleason Grading System (9)



Prostate Cancer Descriptive Epidemiology

Worldwide

PCa is the second most common cancer worldwide in men. In 2012 it is estimated that it accounted for 15% of all cancers diagnosed in men with 1.1 million cases. Incidence rates vary geographically by more than 25 fold (**Figure 4**). 70% of cases occur in the developed world, with highest rates in Australasia and North America. The lowest rates are seen in East and South Central Asia. Higher rates in certain less developed regions, including the Caribbean and Southern Africa, probably reflect ethnic differences rather than differences in prostate specific antigen (PSA) testing and health care systems. However, rates are rising in the developing world, which is likely as a result of increasing westernisation of dietary and lifestyle factors in those areas. Though incidence rates vary widely, mortality rates are more constant worldwide. PCa accounts for 6.6% of total deaths in men and is estimated to have caused 307,000 deaths worldwide in 2012. The highest mortality rates are seen in the predominantly black populations of the Caribbean and Southern Africa as compared to Caucasian populations (10).

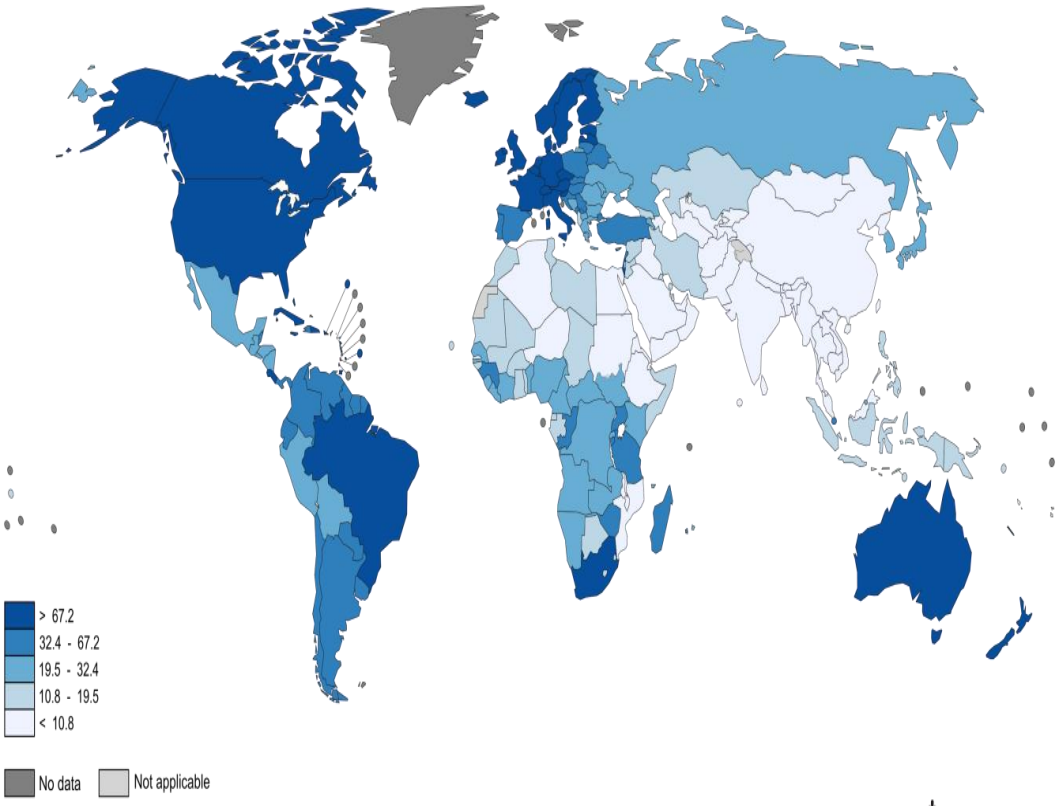
United Kingdom

In the UK PCa is the commonest cancer in men, with approximately 1 in 8 men affected. More than 47,000 men are diagnosed each year and over 330,000 men are living with PCa. There are more than 11,000 deaths per year from PCa (11). The standardised death rate (SDR) per 100,000 inhabitants was 47.6 in the UK in 2013 (12).

Sweden and the rest of Europe

It is estimated that there were over 72,000 deaths from PCa across Europe in 2013. This accounts for 5.6% of all cancer deaths. **Table 1** shows the number of deaths and SDR for PCa across European countries. In Sweden the SDR for PCa for all men was 62.5, which is higher than in the UK. Sweden is also the only European country where the SDR for PCa was higher than the equivalent rate for lung cancer (12).

Figure 4: Estimated PCa incidence worldwide 2012



The boundaries and names shown and the designations used on this map do not imply the expression of any opinion whatsoever on the part of the World Health Organization concerning the legal status of any country, territory, city or area or of its authorities, or concerning the delimitation of its frontiers or boundaries. Dotted and dashed lines on maps represent approximate border lines for which there may not yet be full agreement.

Data source: GLOBOCAN 2012
Map production: IARC
World Health Organization

World Health Organization

Table 1: European PCa Death data for all male residents in 2013 (12)

	Number of deaths	Share of all male deaths	Standardised death rate		
			Males	Males aged < 65 years	Males aged 65 and over
	(number)	(%)	(per 100 000 inhabitants)		
EU-28	72 674	2.9	39.4	2.6	191.4
Belgium	1 457	2.7	37.4	1.8	184.3
Bulgaria	998	1.8	36.3	3.7	170.9
Czech Republic	1 424	2.6	44.8	3.2	216.2
Denmark	1 198	4.6	63.5	3.3	312.0
Germany	13 430	3.1	41.6	3.0	201.3
Estonia	259	3.5	68.7	5.0	331.7
Ireland	502	3.4	45.4	3.4	219.0
Greece	1 588	2.8	32.6	1.4	161.5
Spain	5 785	2.9	33.1	1.9	162.3
France	8 894	3.1	36.9	2.1	180.3
Croatia	740	3.0	54.5	2.5	269.0
Italy	7 193	2.5	27.9	1.4	137.0
Cyprus	99	3.5	44.0	1.6	218.9
Latvia	368	2.7	68.3	4.8	330.3
Lithuania	528	2.6	60.0	5.4	285.4
Luxembourg	43	2.3	29.0	1.5	142.1
Hungary	1 209	2.0	41.9	3.7	199.8
Malta	38	2.3	31.1	2.1	151.2
Netherlands	2 546	3.7	47.5	2.7	232.5
Austria	1 147	3.1	41.0	2.0	201.7
Poland	4 283	2.1	41.5	3.5	198.3
Portugal	1 715	3.2	43.0	2.4	210.6
Romania	2 158	1.7	33.6	2.6	161.3
Slovenia	372	3.9	59.4	3.1	291.5
Slovakia	629	2.3	50.0	4.4	238.5
Finland	852	3.3	44.2	2.5	216.6
Sweden	2 350	5.4	62.5	3.0	308.1
United Kingdom	10 869	3.9	47.6	2.8	232.3
Liechtenstein	4	3.3	33.9	0.0	173.9
Norway	1 006	5.2	61.7	3.0	304.0
Switzerland	1 358	4.4	49.1	2.6	241.0
Serbia	942	1.9	36.0	2.5	174.5
Turkey	3 530	1.8	23.9	1.8	115.6

Prostate Cancer Risk Factors

There are modifiable and non- modifiable risk factors for PCa. Of the established risk factors the most important are all non-modifiable and include: age, race/ethnicity and family history/genetic factors. These and some potentially modifiable risk factors are discussed below.

Age

Like many adenocarcinomas, PCa is strongly associated with increasing age. It is seldom diagnosed in men under the age of 40 and its incidence increases exponentially from the age of 55. In populations with widespread access to PSA testing the average age of PCa diagnosis has shifted forwards, by as much as 10 years. For example, in the USA the median age at diagnosis is 66 years (4).

Race/Ethnicity

PCa incidence and mortality rates vary between different ethnicities, with the highest rates seen in black populations. In SEER data from the USA, mortality rates in black men were nearly 2.5 times higher than in white men. The lowest incidence and mortality rates are seen in Asian populations (4). The average age at diagnosis is also lower in black men compared to white men (13). The reasons for these racial differences are not fully understood, but are likely to be due to a combination of genetic and socioeconomic factors.

Family History and Genetics

Several large family and twin studies have established that family history is a significant risk factor for PCa. The risk increases with increasing number of family members affected. A Swedish study of in 51,897 men who were brothers of 32,807 index cases reported that the overall risk of developing PCa for men with one brother with PCa by age 65 years was 14.9 vs. 4.8 % in those without a brother with PCa, and 30.3 vs. 12.9 % at age 75 years (14). Several studies have also shown that it is not only incidence which clusters in families, but outcomes too (15, 16). Hemminki *et al.* examined the survival in sons according to the fathers' length of survival. The hazard ratio (HR) was 0.62, 95% CI: 0.41-0.94 for sons whose fathers had survived longer than 59 months, compared with sons whose fathers had survived fewer than 24 months. This suggests that family history also affects PCa survival.

Many genetic factors which may contribute to this familial clustering have now been described, but there is no single genetic susceptibility locus or mutation which accounts for the majority of familial cases. Multiple genome-wide association

studies (GWAS) have been conducted to identify common single nucleotide polymorphisms (SNPs) associated with PCa incidence, with more than 100 candidate loci identified (17). However, taken together these SNPs only account for approximately 1/3 of familial PCa cases (4). Germline mutations in both the HOXB13 and BRCA genes have also been shown to be associated with increased risk of PCa (18, 19). Detailed discussion of these mutations is outside of the scope of this thesis.

Diet, Obesity, Activity

Several dietary factors which have anti-oxidant properties have been shown in epidemiological studies to be potentially protective against PCa. These include selenium, vitamin E and lycopene, however data from randomised controlled trials (RCT) into their use as preventative agents is lacking (20). An increased risk of PCa with calcium and dairy products has been suggested by some, but not all studies. One meta-analysis by Gao *et al.* showed a small increase in risk in the highest intake groups of both dairy products and calcium (Relative risk (RR): 1.11, 95% CI: 1.00 to 1.22 and RR: 1.39, 95% CI: 1.09 to 1.77) (21). The relationship between PCa and Vitamin D has also been examined but remains unclear, with both high and low levels being associated with increased risk in some studies (4).

The relationship between obesity and PCa is complex and has been much studied. It is established that obesity is not only associated with a small increased risk of PCa incidence, but also with PCa aggressiveness and outcomes following treatment (22). Some of this association may be explained by difficulties diagnosing and treating obese men, but several biological mechanisms could also explain these associations (**Figure 5**). These include hyperinsulinaemia, increased insulin-like growth factor- 1 (IGF-1) levels, changes in sex hormone levels and chronic sub-clinical inflammation. Chronic inflammation results in a host of changes including altered levels of adiopokines, including leptin. Leptin levels are raised in obesity and have been shown in pre clinical data to increase risk of PCa. However, the epidemiological evidence does not demonstrate a consistent positive association (22). Chronic inflammation also alters the cytokine microenvironment, including increasing levels of IL-6, which has also been linked to increased risk of PCa (22). Furthermore, physical activity has been associated with an inverse risk of advanced PCa in several North American cohort studies (23, 24). The health professional's follow-up study reported no overall association between PCa incidence and total, vigorous or non-vigorous physical activity. However, in all age

groups, men with high levels of physical activity were less likely to be diagnosed with high-grade (Gleason score ≥7) PCa (24).

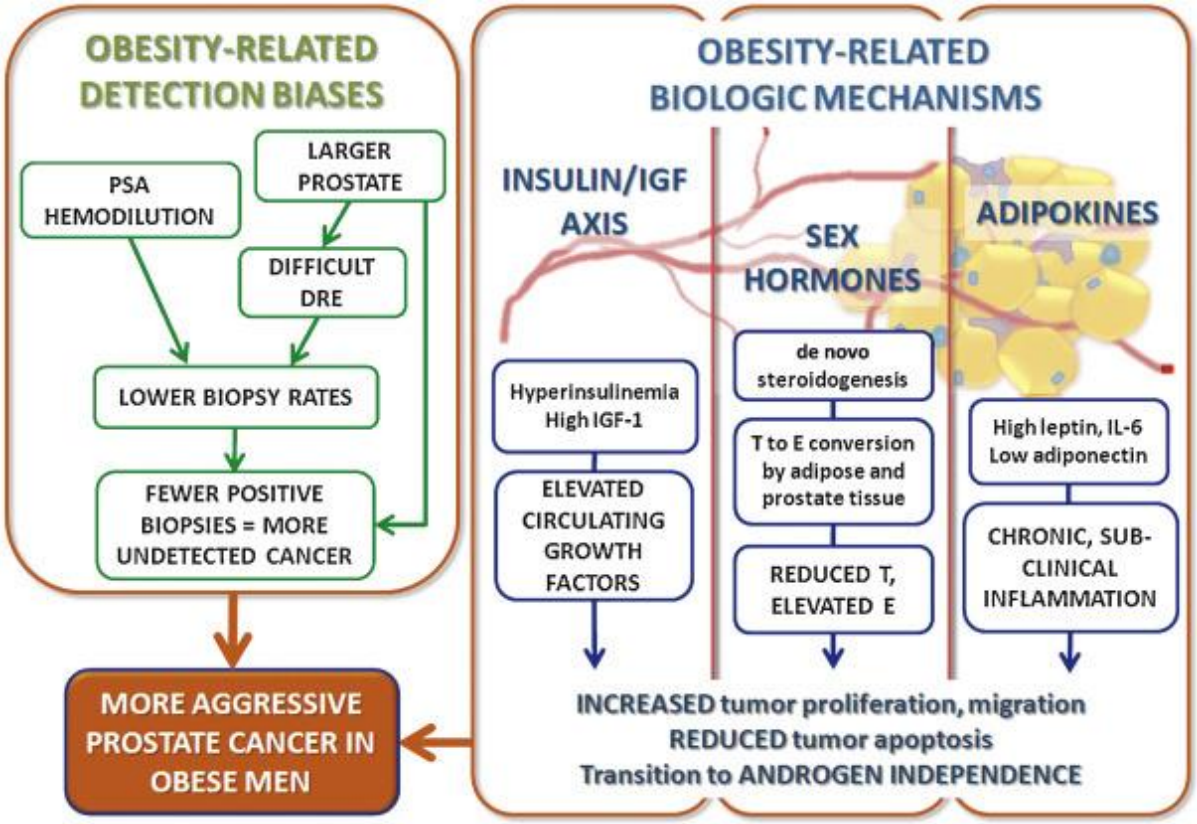
Others

Smoking has been associated with PCa mortality. The largest meta-analysis examining this association included 51 studies and reported an increased risk of PCa death in current smokers (RR: 1.24, 95%CI: 1.18-1.31) as well as a dose response, with heavier smokers having the highest risk (25). This suggests that the multiple carcinogenic compounds included in tobacco accumulate with heavier use and therefore risk increases with increasing exposure.

Coffee consumption has been shown to be associated with a decreased risk of lethal PCa. The health professionals follow up study reported a significant inverse association (RR: 0.82, 95% CI: 0.68 -0.98) after adjustment for age, BMI, physical activity, smoking, family history and dietary factors . The association appears to be related to non-caffeine components of coffee, as it was seen in those drinking both caffeinated and decaffeinated coffee (26).

High levels of alcohol intake have been associated with an increased risk of aggressive PCa (RR: 2.01, 95% CI: 1.33-3.05) after adjustment for age, race amd BMI (27).

Figure 5: Biologic mechanisms contributing to the association between obesity and PCa (22)



Prostate Cancer Clinical Management and Treatment

Screening

PSA is a protein secreted by the prostate gland which increases with age, size of the prostate and also in PCa. Screening for PCa using PSA measurements has been investigated in several large screening trials and remains controversial (28-30). Current international guidelines do not recommend population based PSA screening, as although it reduces PCa mortality (31), this is at the cost of over-diagnosis and over treatment (32).

Symptoms and diagnosis

The majority of PCa is diagnosed following a prostate biopsy prompted by the finding of a raised PSA or an abnormal digital rectal examination (DRE), as most men with early stage PCa are asymptomatic. Men can sometimes present with lower urinary tract symptoms, such as urinary frequency, urgency or nocturia. Less commonly, men can present with haematuria or in advanced disease with bone pain related to metastatic disease.

A transrectal or transperineal prostate biopsy with ultrasound guidance is the gold standard diagnostic technique, but should only be undertaken after considering DRE findings, ethnicity, age, co-morbidities, PSA values, free/total PSA, history of previous biopsy (32).

Staging

If the patient's co-morbidities and general health do not preclude it, further staging investigations should be performed. PCa is staged according to the AJCC TNM staging (**Figure 6**). Localised PCa should then be classified as low, intermediate and high risk disease (**Table 2**). Multi-parametric magnetic resonance imaging (MRI) is an important staging investigation in localised disease to allow an accurate T stage to be obtained. Those with intermediate or high risk disease should also have further investigation with a combination of a technetium bone scan, positron emission tomography-computerized tomography (PET-CT) or whole body MRI to assess for the presence of metastatic disease (32).

Treatment

Management of localised disease

There are several treatment options available for those with localised disease and at present there is no consensus as to which should be the preferred approach. Instead, treatment options are discussed with patients and management is tailored to their individual needs and preferences.

For both low and intermediate risk localised disease, active surveillance (AS) is an option. This consists of close monitoring, using a combination of PSA, MRI and repeat biopsies. There is currently no internationally recognised optimal schedule for AS. The aim of AS is to monitor the PCa and offer active treatment with curative intent to those whose cancer progresses, thereby minimising over-treatment. Curative approaches available include radical prostatectomy (RP), external beam radiotherapy (EBRT) and brachytherapy (32). Watchful waiting (WW) followed by ADT for symptomatic control is another option in those not suitable for more aggressive curative treatments. In patients with high risk or locally advanced disease, options include EBRT with adjuvant ADT or RP with the addition of pelvic lymphadenopathy (32).

Management of advanced/metastatic disease

The gold standard management of advanced/metastatic disease has been continuous ADT. However, recently, data from several large RCTs, including the STAMPEDE trial (33), has shown that the addition of docetaxel chemotherapy to ADT at presentation improves overall survival (OS). This is now the recommended treatment combination in men with hormone sensitive metastatic disease who are fit enough to receive both ADT and chemotherapy (32).

Management of castrate resistant metastatic disease

When a patient with metastatic disease has evidence of disease progression whilst on ADT, with castrate levels of testosterone, they are said to have developed castration resistance. In the last decade several new therapeutic options for this group of patients have emerged. Abiraterone acetate is a steroidal CYP17A1inhibitor which results in the inhibition of androgen synthesis. Enzalutamide is a second generation non-steroidal anti-androgen. The COU-302 trial tested Abiraterone vs. placebo plus prednisolone and reported improved OS (HR: 0.79, 95% CI: 0.66-0.95)(34). The PREVAIL trial tested Enzalutamide vs. placebo and also reported improved OS (HR: 0.71. 95%CI: 0.60-0.84) (35). Both of these second generation hormonal therapies are approved for treatment of castrate resistant metastatic prostate cancer (CRPC) in both the pre and post chemotherapy setting. Docetaxel chemotherapy has also shown improved OS and is another option in patients who are fit enough and have not received it in the hormone sensitive setting (36). Cabazitaxel is also licensed for use in this setting (37). Radium 223 a bone targeted alpha-emitter and Sipuleucel-T, an immunotherapy using activated autologous dendritic cells, are also approved for use, though are used less commonly due to logistical considerations of their administration (32).

Figure 6: AJCC Prostate Cancer Staging 7th Edition (38)

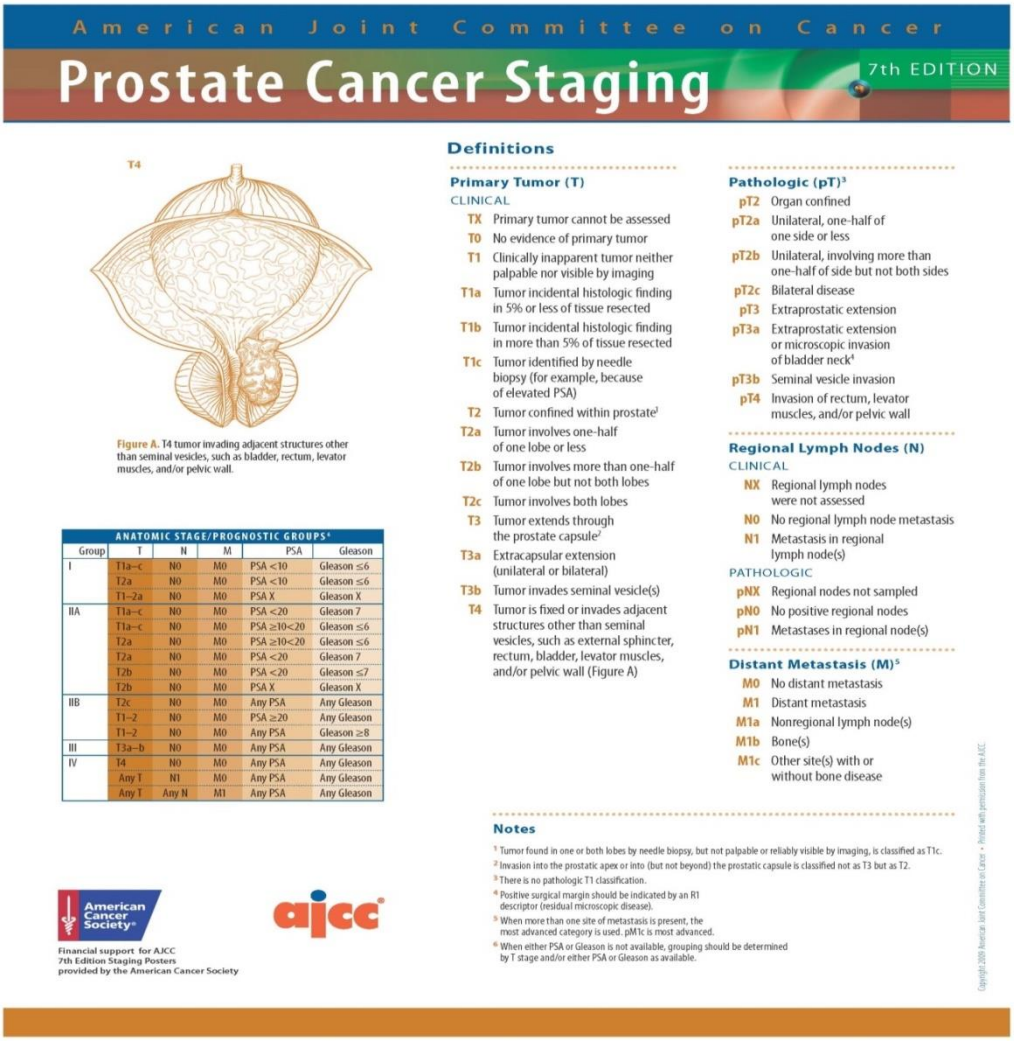


Table 2: Risk groups for PCa from the National Comprehensive Cancer Network Guideline(39)

Low risk	**Local clinical stage T1-2, Gleason score of 2-6 and PSA< 10 ng/ml**
Intermediate risk	T1-2, Gleason score 7 and/or PSA 10-20 ng/ml
High risk	T3 and/or Gleason score 8-10 and/or PSA 20—50 ng/ml

Regionally metastatic/locally advanced	T4 and/or N1 and/or PSA 50-100 ng/ml in the absence of distant metastases (M0 or MX)
Distant metastases	M1 and/or PSA > 100 ng/ml

Type 2 Diabetes Mellitus - biology

Several organs including the pancreas, liver, intestine and kidneys are involved in normal glucose homeostasis (**Figure 7**). T2DM is a metabolic disorder in which there is hyperglycaemia, insulin resistance and relative impairment of insulin secretion. Different individuals have varying degrees of insulin resistance and insulin deficiency, with both contributing to the onset of hyperglycaemia and T2DM. Hyperglycaemia itself impairs the function of pancreatic beta cells which produce insulin and leads to a worsening of insulin resistance, in a vicious cycle of metabolic impairment (40).

Several longitudinal studies have examined insulin resistance and insulin secretion in the years prior to a diagnosis of T2DM. The Whitehall study followed 6,500 non-diabetic civil servants for a median follow up of 9.5 years, during which 505 were diagnosed with T2DM. There was a marked decrease in insulin sensitivity in the five years prior to diagnosis in those who developed T2DM and this was accompanied by an increase in insulin secretion by pancreatic beta cells, in an attempt to compensate for the increasing insulin resistance (41). This process of increasing insulin resistance and secretion results in a period of impaired glucose tolerance, referred to as the pre-diabetic phase, before overt hyperglycaemia develops (**Figure 8**). Insulin resistance is in part due to substances secreted from adipose tissue including leptin, adiponectin and tumour necrosis factor alpha (42). The prevalence of T2DM hence rises markedly with increasing obesity and sedentary behaviours (43).

Figure 7: Organs involved in maintaining plasma glucose (44)

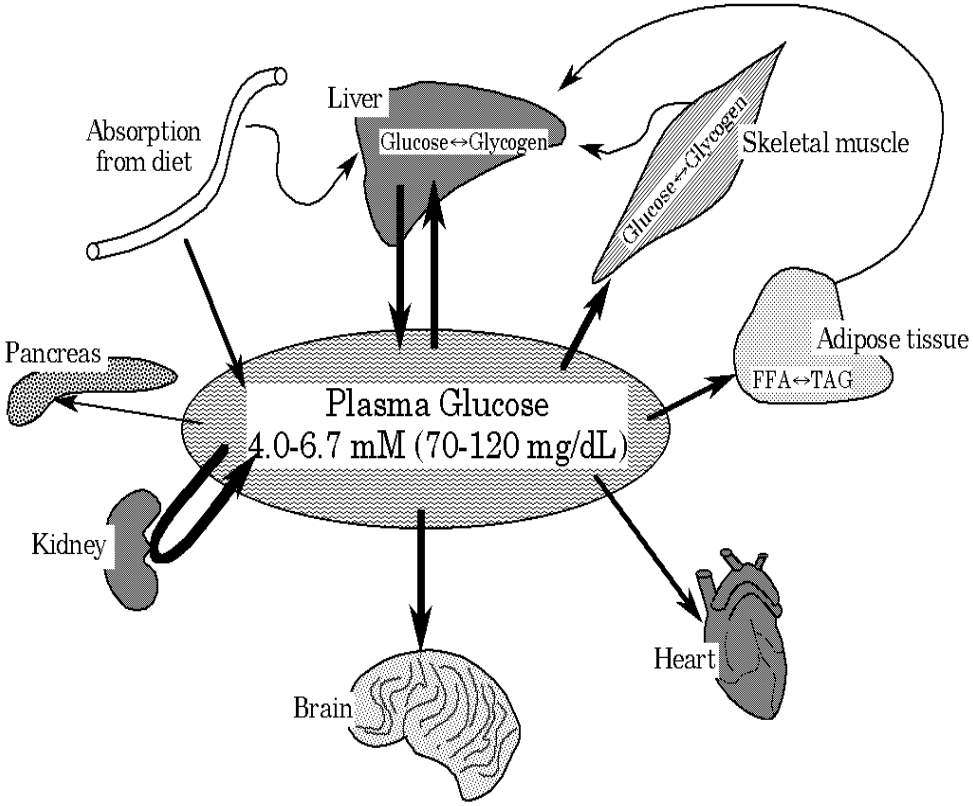
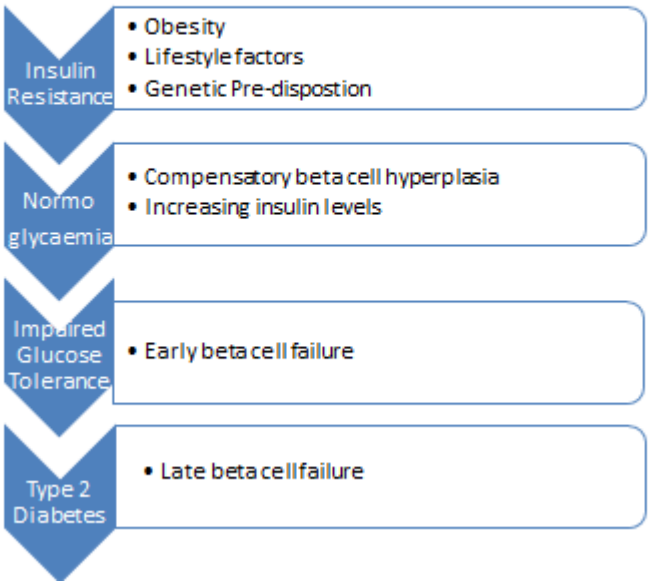


Figure 8: Pathophysiology of Type 2 Diabetes



S

Type 2 Diabetes Mellitus Descriptive - Epidemiology

Worldwide

The number of people with diabetes has risen from 108 million in 1980 to 422 million in 2014. In the same time period the global prevalence among adults has risen from 4.7% to 8.5%. This dramatic increase is due to a rise in the number of cases of T2DM, rather than any change in prevalence of type 1 diabetes (45). The International Diabetes Federation (IDF) estimated that in 2015 seven countries had more than 10 million people with diabetes: China, India, the United States of America; Brazil, the Russian Federation, Mexico and Indonesia (46). Globally, 65% of cases are in urban areas and 35% in rural areas (46). Worldwide in 2015 it has been estimated that T2DM caused 1.6 million deaths (47). It is projected that by 2030 diabetes will be the 7th cause of death worldwide (45). It is also estimated that 1 in 2 people globally with T2DM remain undiagnosed (46).

United Kingdom

The prevalence of diabetes in the UK matches the global trend and is increasing. Since 1996, the number of people diagnosed with diabetes in the UK has more than doubled from 1.4 million to almost 3.5 million (48). Current estimates suggest that 4.5 million people are living with diabetes, with potentially 1.1 million people unaware of their diagnosis. In the UK, T2DM accounts for > 90% of cases of diabetes. The national diabetes audit in 2012 suggested that people with T2DM were 34.5 % more likely to die than those without T2DM, with a Standardised mortality rate (SMR) of 1.34. It is thought that diabetes accounts for 1% of total deaths in the UK (47, 49).

Sweden and the rest of Europe

Similar trends of rising prevalence are seen across Europe. The IDF estimates that in 2015 660 million people within Europe had diabetes and suggest that by 2040 this number will rise to 663 million. Prevalence rates vary widely across the region, with the highest rates seen in Turkey. In 2015 it was estimated that diabetes caused 627,000 deaths across Europe, with slightly more deaths in women compared to men (315,000 vs 312,000,respectively) (46). In Sweden, prevalence increased from 5.8 to 6.8% between 2007 and 2013; from 6.6 to 7.9% in men and from 5.1 to 5.8% in women. The highest rise was in people older than 65 years but was seen across all age categories (**Table 3**). It has been estimated that the prevalence of diabetes will rise in Sweden from 6.8% (2013) to 10.4% by the year 2050, with 940,000 affected inhabitants (50). As elsewhere, mortality rates are higher in those with T2DM than without. However, in Sweden mortality rates in

those with T2DM are falling faster than the general population due to health care provision (50).

Table 3: Prevalence of diabetes in Sweden 2007 to 2013 by age and sex (50)

	Women				Men				Total			
	20–44	45–64	≥65	≥20 years	20–44	45–64	≥65	≥20 years	20–44	45–64	≥65	≥20 years
2007	1.2%	4.6%	11.7%	5.1%	1.5%	7.4%	16.0%	6.6%	1.4%	6.0%	13.6%	5.8%
2008	1.3%	4.8%	12.0%	5.2%	1.5%	7.7%	16.5%	6.9%	1.4%	6.2%	14.0%	6.1%
2009	1.3%	4.9%	12.1%	5.3%	1.5%	7.8%	17.0%	7.1%	1.4%	6.4%	14.3%	6.2%
2010	1.3%	5.0%	12.4%	5.5%	1.6%	8.0%	17.6%	7.4%	1.4%	6.5%	14.7%	6.4%
2011	1.3%	5.1%	12.5%	5.6%	1.6%	8.1%	18.0%	7.6%	1.4%	6.6%	15.0%	6.6%
2012	1.3%	5.2%	12.7%	5.7%	1.6%	8.2%	18.5%	7.8%	1.5%	6.7%	15.3%	6.7%
2013	1.4%	5.2%	12.8%	5.8%	1.6%	8.3%	18.8%	7.9%	1.5%	6.8%	15.6%	6.8%

doi:10.1371/journal.pone.0143084.t002

Type 2 Diabetes Mellitus - Risk factors

As with PCa, there are several known risk factors for the development of T2DM, some of which are non-modifiable, such as age and inherited genetic pre-disposition and others such as lifestyle factors and obesity which are potentially modifiable. The major risk factors are discussed below.

Age

As shown above in **Table 3**, T2DM increases with age, with highest rates seen in those over 65 years old. However, with the increasing levels of childhood obesity across the developed world, prevalence is rising throughout all age categories including in children (50).

Family history and Genetics

Those with a family history of T2DM are at higher risk of developing the condition. The InterAct case-cohort study examined over 13,000 individuals and a family history of T2DM was associated with a higher incidence of T2DM (HR: 2.72, 95% CI: 2.48-2.99). This association was only modestly reduced after adjusting for other established risk factors such as BMI (HR: 2.44, 95% CI: 2.03 - 2.95). An even higher risk was observed for those in whom both parents had T2DM (HR: 5.14, 95% CI: 3.74-7.07) (51). The genetic susceptibility to T2DM is complex and is likely to be polygenic. In one meta-analysis of six GWAS looking for candidate genetic loci, six new loci were identified. These included loci involved in pancreatic cell development and function, as well as some involved in insulin release and action

(52). However, the contribution of these genetic variants to the overall incidence of T2DM is low, with lifestyle and environmental factors playing a more significant role.

Ethnicity

T2DM risk is up to six times higher in those of South Asian ethnicity and three times higher in those of African descent than in white Caucasians (53). This is believed to be due to a combination of environmental and genetic factors. This is the converse to what is seen in PCa, where risk is lowest in South Asian populations. Little has been studied about how ethnicity may impact on the relationship between the two conditions. Polymorphism 17q12 rs4430796 is associated with both T2DM and PCa and increases risk of PCa in South Asian men in particular (54), This suggests potentially South Asian men who develop T2DM may not be protected from PCa, however, further research to explore this is required.

Obesity

It is well established that increasing levels of obesity are associated with an increasing risk of T2DM (55, 56). This is due to the associated changes in the metabolic micro environment, which lead to peripheral insulin resistance. The pattern of fat distribution is also important, with central obesity seeming to be most important. Suggesting that waist circumference may be a more sensitive risk estimator than BMI (57).

Lifestyle Factors including diet

Physical inactivity and sedentary behaviours have been shown to be associated with an increased risk of T2DM, even within the context of a normal BMI (58). Smoking has also been suggested to increase the risk of T2DM, though a causal link has yet to be fully established. In one meta-analysis of 25 studies, current smokers had an increased risk of T2DM compared to non-smokers (RR: 1.4, 95% CI: 1.3-1.6) and a dose effect with increasing levels of smoking was also observed (59). There are several potential biological mechanisms to explain this potential association including that smoking may impair insulin sensitivity, increase the blood glucose concentration and result in increased abdominal fat distribution (60, 61). The type of diet consumed has also been shown to have either protective or detrimental effects on the risk of T2DM. A diet which is high in red and processed meat or high in sugar has been shown to be associated with an increased risk (62, 63). Whereas a healthy diet high in fruit, vegetables and olive oil has been associated with a reduced risk (64).

Type 2 diabetes mellitus - Clinical management and treatment

Screening

Screening is recommended as up to 50% of patients with T2DM remain undiagnosed. The most recent guidelines from the IDF recommend undertaking a screening questionnaire, such as the validated FINDRISC (65) questionnaire, in those with risk factors including: age >45 , family history of T2DM, obesity and increased waist circumference. Those who have a positive screening test should then undergo the diagnostic process described below. In those with a negative screening test it should be repeated every 3 years (66).

Symptoms and diagnosis

Most patients with T2DM are asymptomatic. Symptoms of hyperglycaemia include polyuria and polydipsia, but are rarely seen in those diagnosed with T2DM, which is most commonly picked up following screening tests or routine blood glucose measurements.

Most guidelines now recommend the use of the IDF and WHO diagnostic criteria for T2DM. This includes a fasting glucose of > 7.0 mmol/L or a random glucose >11.1 mmol/L or a glycosylated haemoglobin (HbA1c) > 48 mmol/mol (**Table 4**) (66).

Glycaemic control and targets

The recommended glycaemic target for those with T2DM varies between various clinical guidelines, but most suggest that HbA1c <53 mmol/mol is an acceptable target. If lower levels can be achieved without excess weight loss and hypoglycaemia, then this is preferable (66).

Education

The majority of major T2DM management guidelines recommend that patient education into their condition should be part of the initial management of T2DM. The National institute of clinical excellence (NICE) recommends that all patients be referred to a diabetes education programme which is run by accredited diabetes educators (67).

Lifestyle, Dietary and Obesity Management

It is established that lifestyle changes including increasing physical activity, weight loss and dietary improvements can help in the management of T2DM and enable patients to reach glycaemic targets. However, the exact role they should play in the initial management is not universally agreed upon. The IDF recommend that a

period of 3-6 month of intense lifestyle and dietary modification, supported by patient education, may be appropriate but stress that prolonged periods of hyperglycaemia if these measures are not effective should be avoided. Other guidelines recommend that initial pharmacological management is instituted immediately at diagnosis alongside these measures (66).

Dietary advice to those with T2DM who are overweight or obese is to reduce calorie intake by 500-600 calories, aiming for a daily intake of between 800-1200 calories. Patients should avoid sugar, sweets and sweetened drinks and aim for a high fibre diet. Other important lifestyle advice includes increasing physical activity, smoking cessation and avoiding excess alcohol consumption. Anti-obesity drugs should also be considered in patients with T2DM and a BMI >27 and bariatric surgery should be considered in those with a BMI > 35 (66).

Oral Hypoglycaemics

Metformin (1,1-dimethylbiguanide hydrochloride) is a biguanide oral hypoglycaemic agent (OHA) and is the recommended first line monotherapy in the treatment of T2DM (66, 67). Metformin inhibits gluconeogenesis and reduces circulating levels of insulin (68). The dose should be titrated from 500mg to 2000mg daily. If metformin is not tolerated or contraindicated then there is no established best second option but guidelines recommend one of: a dipeptidyl peptidase-4 (DPP-4) inhibitor, pioglitazone or sulphonylurea (SU).

DDP-4 inhibitors work by inhibiting Glucagon-like peptide-1 (GLP-1). They exert their glucose controlling effects via multiple mechanisms including: enhancement of glucose-dependent insulin secretion, slowed gastric emptying and a reduction of food intake. GLP-1 agonists also have a similar mechanism of action.

Pioglitazone is a thiazolidinedione which bind to and activates peroxisome proliferator-activated receptors (PPARs). PPAR activation causes insulin sensitisation, via a decrease in glucose production and an increase in glucose utilisation (69).

SU stimulates insulin secretion. SU binds to the K-ATP channel in pancreatic beta cells which regulate insulin secretion. This binding leads to calcium influx into the cells and insulin secretion (70).

If monotherapy with metformin or its replacement is not achieving adequate glycaemic control then an additional therapeutic agent should be added. Various

combinations are advised. The various risks and benefits of these different classes of OHA are described in detail in **Table 5**.

Insulin

Initial insulin therapy is recommended only when patients have unstable symptomatic hyperglycaemia. Basal insulin can then be instituted to gain glycaemic control rapidly, before being discontinued in favour of the standard OHAs described above (66). If dual therapy with two OHA has still not gained glycaemic control, then most guidelines recommend the addition of insulin therapy (66).

Table 4: WHO and IDF Diagnostic Criteria for T2DM

Test	Impaired Fasting Glycaemia	Diabetes
Fasting Glucose	6.1-6.9 mmol/L	≥7.0 mmol/L
OR 2 hour glucose following ingestion of 75g glucose load	7.8-11 mmol/L	≥11.1 mmol/L
OR random glucose in symptomatic patient		≥11.1
OR HbA1c		≥6.5% (48 mmol/mol)

Table 5: Risks and Benefits of different classes of OHA taken from the IDF clinical practice recommendations for managing T2DM in primary care (66)

	Metformin	**Sulphonylurea**	**Pioglitazone**
Hypoglycaemia	Neutral	Moderate/Severe	Neutral
Weight	Slight loss	Gain	Gain
CKD[1] stages 3A, 3B	Reduce dose in 3A Contraindicated 3B	Higher risk of hypoglycaemia	Neutral
CKD[2] stages 4,5	Contraindicated	Contraindicated	Neutral
GI side effects**	Moderate	Neutral	Neutral
Other side effects	Benefit	Neutral	Oedema Bone fracture
Major CV[3] events	Neutral	Neutral	Neutral
CHF[4]	Neutral	Neutral	Increased risk

[1] CKD Chronic kidney disease

[2] GI Gastrointestinal

[3] CV Cardiovascular

[4] CHF Chronic heart failure

Metabolic Syndrome - Biology

MetS is a cluster of disorders including central obesity, hypertension, impaired glycaemia and dyslipidaemia. There are various definitions including those proposed by the World Health Organisation (71), National Cholesterol Education Program and Adult Treatment Panel III (72) and the IDF (73). See **Table 6** for comparison of these definitions. The joint statement of major international associations (74) defines everybody with three of the following metabolic risks: impaired glycaemia, obesity, dyslipidaemia or hypertension as having MetS.

MetS is associated with a pro-inflammatory state with raised levels of C-reactive protein (CRP) and interleukin (IL)-6, which is a proposed biological mechanism by which MetS causes an increase in subsequent cardiovascular disease (CVD) and T2DM (75, 76). Another proposed mechanism is that MetS causes a pro-thrombotic state, with elevated levels of plasminogen activator inhibitor (PAI)-1(77).

Metabolic Syndrome - Descriptive epidemiology

As described above the worldwide prevalence of T2DM and obesity continues to increase dramatically. In a US study, using data from the National Health and Nutrition Examination Survey (NHANES), the prevalence of MetS increased by more than 35% between the periods1988–1994 to 2007–2012, from 25.3% to 34.2% (78). Therefore, mirroring the global trends for obesity and T2DM. Though statistics are not widely collected on the prevalence of MetS, the IDF estimates that 20-25% of the worlds adult population may have MetS and that they are twice as likely to die from CVD or a stroke than those without the syndrome (73).

Metabolic Syndrome - Risk factors

Obesity

Obesity is an important risk factor for MetS. In data from the large US NHANES study, MetS was present in only 4.6% of normal weight men but in 22.4%, and 59.6% of overweight and obese men, respectively (79). In a further US study, increasing waist circumference was also associated with an increasing risk of MetS (age, sex and ethnicity adjusted OR: 1.7, 95% CI: 1.3-2.0 per 11 cm) (80). This highlights the importance of fat distribution in MetS, with central obesity being a significant component.

Ethnicity and Others

Race also appears to be a risk factor for developing MetS. The NHANES study demonstrated increased risk in those of Mexican ethnicity, with lowest rates in Black Americans. These differences persisted even after adjusting for age, body

mass index (BMI), and socioeconomic status (78). Some other postulated risk factors include smoking (79), low income (79) and physical inactivity (81).

Metabolic Syndrome - Clinical management and treatment

Primary intervention

Once identified, MetS should be treated to reduce the risk of T2DM and CVD. Primary intervention is with lifestyle changes including:

1. Moderate calorie restriction (to achieve a 5–10 per cent loss of body weight in the first year)
2. Moderate increase in physical activity
3. Diet modification to high fibre, low sugar and fat diet (73)

The primary aim of these lifestyle changes should be weight loss, which has been shown to delay or reduce the onset of T2DM in high risk, obese individuals with impaired fasting glucose. In the Finnish Diabetes Prevention study, 522 middle aged, overweight subjects with impaired glucose tolerance were randomised to standard care or an intensive lifestyle intervention group. The intervention included dietary counselling and circuit-type resistance training sessions. Those in the intervention group had significantly more weight loss after one and three years, as well as improved glucose and lipid measurements compared to the standard care group (82).

Secondary Intervention

For those patients in whom MetS persists after the institution of lifestyle measures, pharmacological intervention is recommended. At present this management is aimed at the individual components of the syndrome. This includes anti-hypertensives to treat established hypertension, though no particular class has been shown to be beneficial in MetS. Dyslipidaemia management aiming to lower low density lipoproteins (LDL) and triglycerides (TGs) and raise high density lipoprotein (HDL) .Statins and fibrates should also be considered if appropriate. Finally, the American diabetes prevention programme has shown that metformin can reduce the development of T2DM in those with impaired fasting glucose. 3,234 non diabetic persons with elevated fasting glucose were randomised to placebo, metformin (850 mg twice daily), or a lifestyle-modification programme. They reported that the lifestyle intervention reduced the incidence of T2DM by 58 % and metformin by 31 % as compared with placebo (83). This suggests that metformin may be a useful therapeutic option in those who have not been able to make lifestyle changes successfully.

Table 6: Comparison of the World Health Organisation (WHO), National Cholesterol Education Program and Adult Treatment Panel III (NCEP ATP III) and International Diabetes Federation (IDF) definitions of Metabolic Syndrome.

	WHO	NCEP ATP III	IDF
Definition	Impaired Glycaemia/T2DM[1] + 2 other criteria	3 of 5 criteria present	Central Obesity + 2 other criteria
Glycaemia	Impaired glucose regulation or T2DM	Fasting glucose >110 mg/dL	Fasting glucose >100-125mg/dL or T2DM
Obesity (WC[2] / WHR[3])	WHR: Men >0.90 cm Women> 0.85 cm	WC: Men >102cm Women > 88cm	WC with ethnic specific values
Lipids TG / HDL[4]	TG > 150mg/dL Men HDL < 35mg/dL Women HDL <39mg/dL	>150 mg/dL	TG > 150 mg/dL Men HDL <40mg/dL Women HDL <50 mg/dL Or specific treatment for lipid abnormality
Hypertension	>160/90 mmHg	>130/>85 mmHg	On treatment or BP >130/85 mmHg

1 - T2DM- Type 2 Diabetes Mellitus
2 - WC- Waist circumference
3 - WHR- Waist Hip ratio
4- TG- Triglycerides; HDL- High density Lipoprotein

Chapter III: Prostate Cancer and Type Two Diabetes Mellitus

Introduction

As described above, PCa remains the commonest cancer in men, affecting one in eight men in the UK. There are also 3.2 million people in the UK who have been diagnosed with T2DM and it is estimated that this will rise to 5 million by 2025 (2). PCa and T2DM thus often occur together in the same individual.

However, the relationship between them is much more complex than just two prevalent co-existent conditions. It is established that T2DM increases the risk of cancer-specific death from several solid malignancies, including colorectal and breast cancer (84); but conflicting evidence exists in the case of PCa. The impact of pre-existing T2DM has also been studied in regards to grade and stage of PCa at presentation, with conflicting results (85). Moreover, there is emerging evidence that the presence of T2DM and other metabolic abnormalities (dyslipidaemia, hypertension, and obesity) are associated with a more rapid progression of PCa (86, 87). This relationship is further complicated by the fact that standard treatment for advanced PCa, ADT, has been suggested to increase incidence of T2DM (88), as well as worsen glycaemic control in those with pre-existing T2DM.

To provide a background on the complex association between PCa and T2DM, this chapter is set out to explore the following areas:

1. Impact of pre-existing T2DM on PCa incidence
2. Impact of pre-existing T2DM on PCa grade and stage
3. Impact of pre-existing T2DM on PCa outcomes and mortality
4. Interplay between T2DM and PCa treatments

Impact of pre-existing T2DM on PCa incidence

It is now well established that T2DM increases risk of some solid malignancies, although not all the literature supporting this is robust (89). Some studies suggest that people with T2DM are as much as twice as likely to die from cancer than those without (84). However, the opposite is seen in PCa, with an inverse association reported in several published meta-analyses (89).

Bonovas *et al*. published the first meta-analysis examining T2DM and risk of PCa in 2004. They included fourteen studies and concluded that T2DM confers a statistically significant 9% decrease in relative risk of developing PCa (90). This was followed in 2006 by a meta-analysis conducted by Kasper *et al*. which included 19 studies and reported an inverse relationship of a similar magnitude, RR: 0.84, 95%CI: 0.76-0.93 (91). Following this, Bansal *et al*. published an updated meta-analysis including 45 studies, involving 8.1 million participants and 132,331 PCa cases, which also reports an inverse association with a RR of 0.86 (95% CI 0.80-0.92) (92). More recently, Gang *et al*. published a further updated meta-analysis reviewing the literature up to and including April 2012. This meta-analysis included 56 studies and also reported an inverse association, RR: 0.88 ,95%CI: 0.82-0.93 (93). Here, I performed a further systematic review of the literature up until June 2017.

Evidence Acquisition

The systematic review was performed in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) guidelines (94), with search terms, inclusion and exclusion criteria all defined a priori.

Search Strategy

A computerised literature search of Pubmed to identify full text and abstracts published was performed with and without MESH terms (diabetes, diabetes mellitus, prostate cancer, prostate neoplasm, incidence, risk). All references of the selected articles were checked, including hand searches.

Study Eligibility

The final articles were chosen based on the following set of inclusion criteria:

- Examined the association of T2DM with PCa incidence/risk
- Case control or cohort study
- English Language
- Not included in the prior published meta-analyses described above

Studies were excluded if they:

- Examined the association of T2DM with PCa mortality
- Examined the association of T2DM treatments (i.e. drugs) and PCa incidence
- Were a review article or meta-analysis

Initially, titles were reviewed to assess whether they met inclusion criteria. If, after assessing the abstract, there was any doubt regarding its suitability for inclusion, it was kept for more thorough, subsequent assessment. The list of potential articles was further shortened by performing detailed evaluations of the methods and results of each remaining paper. **Figure 9** provides more detailed information regarding the exclusion process. The strength of each study was assessed using the strengthening the reporting of observational studies in epidemiology (STROBE) criteria (95) and is presented in **Figure 10**.

Data collection

The following details were recorded for each study: author, year of publication, country where study was undertaken, study design, number of patients, population/setting, outcome reported and variables adjusted for in the analysis.

Evidence synthesis

The literature search identified a total of 896 studies of which 44 were deemed as initially relevant. Using the above inclusions and exclusion criteria, 36 were excluded (**Figure 9**). The reasons for exclusion were: included in previously published meta-analysis (22), only T2DM patients included (6), full article not available (3), outcome not PCa incidence (2), meta-analysis (1), duplicate data (1), genetic variant of T2DM examined only (1) (**Figure 9**). A total of eight studies were included in the systematic review (**Table 7**).

Of these eight studies, five were cohort studies (96-101) and three were case-control studies (102, 103). Three studies were from European populations, two from the USA, two from Israel and one from Australia.

The studies combined included 2,716,302 subjects. Six reported an inverse association between T2DM and PCa incidence (96-100, 103), one reported no association (102) and in one a positive association was reported (101). Of the six studies reporting an inverse association, they all reported similar measures of association in the magnitude of a 20% reduction in risk of PCa in those exposed to

T2DM as compared to those without T2DM. The one paper which reports no statistically significant association is a case-control study in which cases of T2DM were patients enrolled in the Freemantle Diabetes Study (102). It is the smallest of the studies included here, with 1,289 cases and 5,156 controls - which may account for the non-statistical significance of their findings (sub hazard HR: 0.83, 95%CI: 0.60-1.14), though the direction and magnitude of the association reported is in line with the other studies. The study which reported a positive association is a retrospective review of 3,162 consecutive men who underwent a prostate biopsy due to either an elevated PSA and/or an abnormal DRE (101). This design is different to the others studies included here, which were largely based on the general population, not on a selected population attending for a prostate biopsy. This heterogeneity in the design may account for the findings of a 26% increased odds of a positive biopsy in patients with T2DM, compared to those without (Odds ratio (OR): 1.26 95%CI: 1.01-1.55). The biological explanation for this finding is discussed further below.

Discussion

The biological mechanism underlying the inverse association between T2DM and PCa risk is not elucidated. Firstly, several metabolic alterations occur in people with T2DM which may protect from PCa. The Insulin-IGF-1 theory of carcinogenesis suggests that prolonged hyperinsulinaemia results in reduced insulin binding proteins and therefore increased free IGF-1, which results in cellular changes which can lead to carcinogenesis via increased mitosis and decreased apoptosis (104). There is both laboratory and epidemiological evidence supporting that raised insulin levels are associated with increased PCa risk (105, 106). Patients with T2DM, though initially may have raised insulin levels, over time develop hypoinsulinaemia. Hence patients with T2DM who have lower levels of insulin over time would be protected in terms of PCa risk (107). Several studies have reported a strengthening of the inverse association between T2DM and PCa risk with duration of T2DM (108-110), which serves to strengthen this hypothesis. Prolonged hypoinsulinaemia may also result in a reduction of leptin, a hormone involved in energy homeostasis (111), raised levels of which have been associated with PCa risk (112, 113). However, there are no published studies specifically examining this relationship between insulin and leptin levels in T2DM and risk of PCa.

Another metabolic change which occurs in T2DM is a reduction in testosterone levels which has been shown both in vitro and in vivo (114, 115). PCa is

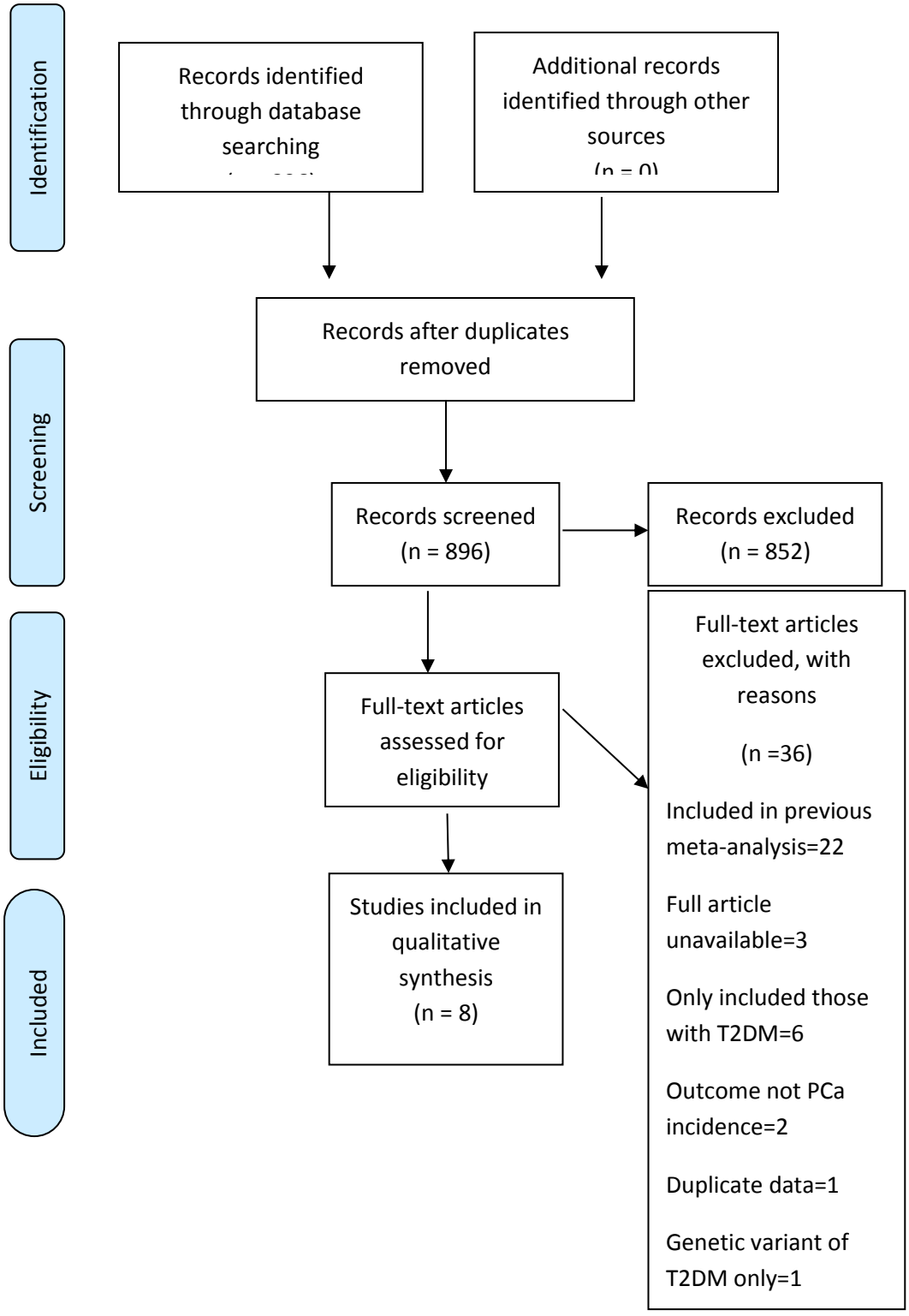
testosterone driven (116), therefore a decrease in testosterone is expected to be associated with a decreased risk.
Genetic factors as well as metabolic changes have also been postulated to be involved in the protective effect which T2DM appears to have on PCa risk. The TCF2 gene confers a predisposition to T2DM and has also been shown to have a potential protective effect in PCa. Similarly, other studies have identified different variants in the JAZF1 gene, one associated withT2DM and another associated with PCa (117).

Some cross-sectional studies have shown that men with T2DM have lower PSA levels, compared to those without T2DM (118) and the rate of change over time is also lower (119). This could result in less screen detected PCa and at least in part account for the difference in risk seen. This is supported both by studies in which enrolled participants undergo prostate biopsy, which report increased risk of positive biopsies in T2DM (101), and by those which show higher grade PCa detected in those with T2DM (85).
Finally, treatments used for T2DM, including metformin, could be potential confounders in the association between T2DM and PCa risk, this is discussed later in this chapter.

Conclusion

The updated systematic review of the literature examining the association between T2DM and PCa risk presented here concurs with the previously published findings of several meta-analyses, indicating that T2DM has a protective effect on PCa risk. However, the underlying biological mechanisms are yet to be elucidated.

Figure 9: Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) flow diagram of article identification, screening, eligibility and inclusion for systematic review on impact of T2DM on PCa incidence.



Author, Year, Country	Study Design	No of patients	Population/Setting	Outcome Reported	Adjusted for
Dankner, R, 2016, Israel	Retrospective Cohort	2,186,196	Men aged 21-89 covered by a large Health Care Provider	T2DM inversely associated with PCa HR: 0.80; 95%CI: 0.76-0.85	age, ethnicity, socioeconomic status
Tsilidis K, 2015, Europe	Prospective Cohort	139,131	Men aged 35-70 from general population	T2DM inversely associated with PCa HR: 0.74; 95%CI: 0.63–0.86	Education, smoking, BMI, Waist circumference, physical activity
Lai, G, 2013, USA	Prospective Cohort	295,276	Men aged 50-71 in 6 US States , general population	T2DM inversely associated with PCa HR: 0.74; 95%CI: 0.70-0.78	age, BMI, race, education, marital status, education, family history Cancer, Diet, Smoking
Lawrence,YR, 2013, Israel	Prospective cohort within RCT	11,541	Men aged 36-74 with coronary heart disease enrolled in a secondary prevention trial	T2DM inversely associated with PCa HR: 0.54; 95%CI: 0.40-0.73	fasting glucose, Triglycerides, HDL, blood pressure ,insulin, tobacco, metformin
Fall, 2013, Sweden	Nested case control	44,352	Men from PCBaSe Sweden	T2DM inversely associated with PCa OR: 0.80; 95%CI: 0.76-0.85	socioeconomic status, marital status, comorbidity, age at PCa diagnosis,

					Prevalence of DM in county
Magliano DJ, 2012, Australia	Case Control	1289 cases 5156 controls	Cases from Fremantle Diabetes Cohort Study and controls from general population	No significant association reported HR: 0.83; 95%CI: 0.60-1.14	age, sex , post code matched controls
Attner B, 2012, Sweden	Case Control	3,545 cases 26,654 controls	Cases from Cancer register Southern Sweden , Controls from general population	T2DM inversely associated with PCa RR: 0.81; 95%CI: 0.72-0.93	age, sex , county matched controls
Moses KA, 2012, USA	Retrospective cohort	3162	Men referred for a Prostate biopsy because of abnormal DRE and/or abnormal PSA	T2DM associated with an increased odds of positive biopsy OR: 1.26; 95%CI: 1.01-1.55	age, race, BMI, prostate volume, family history, PSA, DRE, interaction PSA and DRE

Table 7: Characteristics of the eight studies included in the systematic review on impact of T2DM on PCa incidence.

Figure 10: Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) checklist for observational studies included in the systematic review on impact of T2DM on PCa incidence.

	Item No	Recommendation	Dankner 2006	Tsilidis 2015	Lai 2013	Lawrence 2013	Fall 2013	Maglia no 2012	Attner 2012	Moses 2012

Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	☒	☐	☒	☐	☒	☒	☒	☒
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	☒	☒	☒	☒	☒	☒	☒	☒
Introduction										
Background/ rationale	2	Explain the scientific background and rationale for the investigation being reported	☐	☒	☐	☒	☒	☒	☒	☒
Objectives	3	State specific objectives, including any pre specified hypotheses	☒	☒	☒	☒	☒	☒	☒	☒
Methods										
Study design	4	Present key elements of study design early in the paper	☒	☒	☒	☒	☒	☐	☒	☒
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	☒	☒	☒	☒	☒	☒	☒	☒
Participants	6	(*a*) *Cohort study*—Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up	☒	☒	☒	☒	*n/a*	*n/a*	*n/a*	☒
		Case-control study—Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls	*n/a*	*n/a*	*n/a*	*n/a*	☒	☒	☒	*n/a*

		(*b*) *Cohort study*—For matched studies, give matching criteria and number of exposed and unexposed	☒	☒	☒	☒	*n/a*	*n/a*	*n/a*	☒
		Case-control study—For matched studies, give matching criteria and the number of controls per case	*n/a*	*n/a*	*n/a*	*n/a*	☒	☒	☒	*n/a*
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	☒	☒	☐	☒	☒	☒	☐	☒
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	☒	☒	☐	☒	☒	☒	☐	☒
Bias	9	Describe any efforts to address potential sources of bias	☐	☒	☒	☒	☒	☒	☐	☒
Study size	10	Explain how the study size was arrived at	☒	☐	☐	☐	☐	☐	☐	☐
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	*n/a*	☒	*n/a*	☒	☒	☒	*n/a*	☒
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	☒	☒	☒	☒	☒	☒	☒	☒
		(*b*) Describe any methods used to examine subgroups and interactions	☒	☒	☒	☒	☒	☒	☒	☒

		(*c*) Explain how missing data were addressed	☐	☒	☐	☐	☐	☐	☐	☒
		(*d*) *Cohort study*—If applicable, explain how loss to follow-up was addressed	☐	☒	☒	☐	*n/a*	*n/a*	*n/a*	☒
		Case-control study—If applicable, explain how matching of cases and controls was addressed	*n/a*	*n/a*	*n/a*	*n/a*	☒	☒	☒	*n/a*
		(*e*) Describe any sensitivity analyses	☒	☒	☒	☒	☒	☒	☒	☒
Results										
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	☒	☒	☐	☒	☒	☐	☐	☒
		(b) Give reasons for non-participation at each stage	☐	☐	☐	☐	☐	☐	☐	☐
		(c) Consider use of a flow diagram	☒	☐	☐	☐	☐	☐	☐	☐
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	☒	☒	☐	☒	☒	☒	☐	☒
		(b) Indicate number of participants with missing data for each variable of interest	☒	☒	☐	☐	☐	☐	☐	☒
		(c) *Cohort study*—Summarise follow-up time (eg, average and total amount)	☒	☒	☐	☒	*n/a*	*n/a*	*n/a*	*n/a*

Outcome data	15*	*Cohort study*—Report numbers of outcome events or summary measures over time	☒	☒	☐	☒	*n/a*	*n/a*	*n/a*	☐
		Case-control study—Report numbers in each exposure category, or summary measures of exposure	*n/a*	*n/a*	*n/a*	*n/a*	☒	☒	☒	*n/a*
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	☐	☒	☐	☐	☐	☒	☒	☒
		(*b*) Report category boundaries when continuous variables were categorized	*n/a*	☒	*n/a*	☒	☒	☒	*n/a*	☒
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	☐	☐	☐	☐	☐	☐	☐	☐
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	☒	☒	☒	☐	☒	☒	☐	☒
Discussion										
Key results	18	Summarise key results with reference to study objectives	☒	☒	☒	☒	☒	☒	☒	☒
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	☒	☐	☒	☒	☒	☒	☒	☒

Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	☒	☒	☒	☒	☒	☒	☒	☒
Generalisability	21	Discuss the generalisability (external validity) of the study results	☒	☐	☐	☒	☐	☒	☐	☐
Other information										
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	☒	☒	☒	☒	☒	☒	☒	☐

Impact of pre-existing T2DM on PCa grade and stage

As discussed in the introduction chapter of this thesis, PCa severity can be described in terms of its grade and its clinical or TNM stage. Some studies have examined whether pre-existing T2DM is associated with a particular grade or stage of disease. In the systematic review of T2DM and PCa incidence (above) including studies published after 2012, of the eight new studies identified, only two presented subgroup analysis on stage and/or grade (96, 99) (**Table 8**). These are discussed below but another systematic review was not deemed informative, as one including literature up until 2013 has previously been published (85).

Existing Literature

In 2013, Xu *et al*. undertook a meta-analysis of all studies examining the association between T2DM and PCa risk including subgroup analysis by different grade and stage (85). They included nine studies: five examining stage only, two grade only and two which explored both. They reported findings of an inverse association between T2DM and PCa for both low and high grade PCa, defined as Gleason 2-6 and Gleason 7-10 (RR: 0.74, 95%CI: 0.64-0.86 and 0.78, 95%CI: 0.67-0.90). They reported a RR of a similar direction and magnitude for localised and advanced disease (RR: 0.72, 95%CI: 0.68-0.76 and 0.85, 95%CI: 0.75-0.97). This meta-analysis included all studies published up until October 2012.

Updated Literature review

Two new studies were identified in the systematic review described above which specifically considered stage and grade of PCa. A nested case-control study by Fall *et al*. included 44,352 men with PCa in Prostate Cancer data Base Sweden (PCBaSe) Sweden, which is based on the National Prostate Cancer register of Sweden (NPCR) (120). They showed an inverse association between T2DM and risk of PCa across all risk groups, low, intermediate and high risk/metastatic (OR: 0.71, 95%CI: 0.64-0.80; 0.76, 95%CI: 0.69-0.84; 0.86, 95%CI: 0.80-0.93, respectively). Whilst they showed a slightly less clear risk pattern for those with high risk and metastatic disease, no significant difference between T2DM and risk category of PCa emerged from this study.

Tsilidis *et al*. included 139,131 men from the European Prospective Investigation into Cancer and Nutrition (EPIC) prospective cohort, 4,531 of whom went on to develop PCa. They reported no statistical evidence for an inverse association between T2DM and PCa risk groups. There was no evidence that the association differed by stage (p-heterogeneity, 0.19) or grade (p-heterogeneity, 0.48) of the

disease, although the numbers were small in some subgroups and the study may have been under powered to detect differences.

Conclusion

The meta-analysis by Xu *et al*. (85) concluded that the protective effect of T2DM on PCa risk is seen across different disease grades and stages – however the number of studies available are too small to confirm this finding. The two new studies identified in the systematic review of T2DM and PCa incidence presented above which considered stage and grade (96, 99) reported similar findings of no significant difference between different stages and grades of PCa. However, sample sizes remain small and no definitive conclusion can be drawn on the impact of T2DM on risk of PCa of different grades and stages. Larger studies are required to address this question in detail.

Table 8: Overview of the eight papers included in the systematic review on T2DM and PCa incidence, by subgroup analysis including PCa stage and grade.

Author/Year/Country	PCa stage	PCa grade
Dankner, R, 2016, Israel	No	No
Tsilidis K, 2015, Europe	Yes	Yes
Lai, G, 2013, USA	No	No
Lawrence,YR, 2013, Israel	No	No
Fall, 2013, Sweden	Yes	Yes
Magliano DJ, 2012, Australia	No	No
Attner B, 2012, Sweden	No	No
Moses KA, 2012, USA	No	No

Impact of pre-existing T2DM on Prostate Cancer outcomes and mortality

Introduction

In 2008, a systematic review and meta-analysis examining all-cause mortality in cancer patients reported worse outcomes in cancer patients who had pre-existing diabetes mellitus (DM) (121). However, the magnitude of the association varied widely between different types of malignancy. This led to a call for research

focusing on individual cancer types. Following this, a body of literature has emerged and three published meta-analyses have examined the association between pre-existing DM and PCa specific and all-cause mortality (122-124). The most recent of which was published in 2016. Much of this literature does not distinguish between type 1 and type 2 diabetes; hence in this section DM is referred to, encompassing both types, unless otherwise specified.

Existing Literature

In 2010, Synder *et al*. performed a systematic review of the literature (seven papers), but was only able to include four studies in a meta-analysis. They could only investigate all-cause mortality and reported a pooled HR: 1.57, 95%CI: 1.12-2.20 for DM versus no DM. They concluded that more rigorous research was necessary before firm conclusions could be drawn.

Subsequently, a further meta-analysis by Cai *et al*. (123) was published in 2015, which included 11 cohort studies and looked at outcomes of all-cause mortality, PCa specific mortality and non PCa mortality. It reported that DM was positively associated with all three outcomes, with pooled HR: 1.50, 95%CI: 1.25-1.79, 1.26, 95%CI: 1.20-1.33, 1.83, 95%CI: 1.33-2.52, respectively. They concluded that DM was associated with an adverse prognosis in PCa and that clinicians treating patients with both conditions should pay more attention to the dual diagnosis and even consider more aggressive treatment strategies.

The final and most recent meta-analysis by Lee *et al*. (124) included 17 cohort studies which included 274,677 men. The studies were mainly from the USA (eight) and Europe (six), with two from Taiwan and one from Korea. They reported a 29% increase in PCa-specific mortality (95%CI: 1.37-2.96), alongside a 37% increase in all-cause mortality (95%CI: 1.29-1.45). They were able to perform a subgroup analysis of three cohort studies which considered T2DM separately from type 1 DM. This analysis showed a two fold increase in all-cause mortality for those with T2DM as compared to those without DM (95%CI:1.37-2.96), and could not exclude a positive association with PCa-specific mortality (RR:1.17, 95%CI: 0.96-1.42).

Evidence Acquisition

As the meta-analysis by Lee *et al* was published within the last year, a full systematic review of the literature was not deemed valuable. However, I reviewed the literature since 2016 searching Pubmed using terms (with and without MESH terms): PCa, DM, prognosis and mortality. Only one new paper was identified (125).

Evidence synthesis

The additional study identified by Zaorsky *et al*. was a retrospective cohort study of 3,217 men with localised PCa undergoing curative radiotherapy. Patients were divided into five groups: 1) No T2DM (n=2,603); 2) T2DM on OHA including metformin (n=251); 3) T2DM OHA not including metformin (n=148); 4) T2DM on insulin (n=89); 5) T2DM - diet controlled (n=126). They examined several outcomes including OS, freedom for biochemical failure and cancer specific survival. They showed an increased overall mortality in those on insulin (HR: 2.06, 95%CI: 1.17-3.63) or with diet controlled T2DM (HR: 2.01, 95%CI: 1.24-3.26), but only an increase in PCa- specific mortality for those on insulin (HR: 3.91, 95%CI: 1.22-11.46). These findings may suggest that OHAs are potentially protective in PCa, the relationship between metformin and PCa is discussed in detail later in this chapter. Whilst interesting, this study contained relatively small numbers in each treatment subgroup making it difficult to interpret the results. It also addressed a slightly different research question than the previously discussed meta-analysis focusing in more detail on the treatment for T2DM, rather than just the presence of absence of T2DM.

Discussion

All three meta-analyses showed an increase risk of all-cause mortality for patients with DM compared to those without. The magnitude varied from a 37% to 57% increased risk. T2DM increases cardiovascular mortality amongst a multitude of other consequences; increased all-cause mortality for those with T2DM is expected. The evidence for PCa-specific mortality is less clear. Both meta-analyses that examined this reported an increased risk in the order of 25-30%, however when only studies which included those with T2DM and not type 1 DM were analysed this increased risk was not statistically significant – though sample sizes were small for these subgroup analyses. In the age group affected most commonly with PCa, T2DM is more prevalent than type 1 DM, and so it is assumed that T2DM is largely contributing to the increases in both all-cause and PCa-specific mortality demonstrated.

A further limitation of the existing literature is that some studies failed to adjust for PCa stage or grade, which is an important which is an important co variate associated with PCa mortality (7). This means that positive associations reported in these studies could be due to failure to adjust for other important co variates, rather than a true effect of DM. Duration and severity of DM are also important co variates which are often not adjusted for. Bensimon *et al*. (126) reported a 23% increased

risk of PCa-specific mortality and a 25% increased risk of all-cause mortality in those with T2DM. They also examined the effect of duration of T2DM and found a peak increase in PCa risk between 2-8 years. They also performed a sensitivity analysis whereby they excluded those people who developed T2DM during follow up, as this could have diluted the risks seen, however, this made no difference. A further limitation of the existing literature is the lack of any competing risk analysis.

Conclusion

The existing literature indicates that T2DM is associated with increased risk of all-cause and may also increase PCa-specific mortality. However, limitations in studies hitherto preclude reliable estimates of what the real sizes of the associations are, especially for PCa-specific mortality.

Interplay between T2DM and PCa treatments

Androgen Deprivation therapy and risk of T2DM

ADT is widely used in the management of PCa. It is the recommended first line treatment in all men with advanced disease, as well as in men with high risk disease following radical radiotherapy (127). Even when PCa progresses to a castrate resistant phenotype, it is recommended that treatment with ADT continues, alongside the addition of further therapies. Given the prolonged clinical course of many men with PCa, they can remain on ADT for many years, making any side effects associated with treatment potentially significant.

Common adverse effects of ADT include fatigue, hot flushes and sexual dysfunction (128). ADT also increases the risk of cardiovascular disease (129) (130), reduced bone mineral density (131) and several North American cohorts have demonstrated an increased risk of DM (88, 132-134). This led the Food and Drug Administration (FDA) in 2010 to require a risk label on all GnRH agonists for increased risk of DM and certain cardiovascular diseases (myocardial infarction, sudden cardiac death and stroke) (135).

ADT has been shown to induce a metabolic-like syndrome, in which patients have decreased insulin sensitivity and increased body fat (136). I have previously undertaken a meta-analysis, including nine published studies, to quantify the association between ADT and MetS (137). The RR of MetS for those on ADT compared to PCa men not on ADT was 1.75, 95% CI: 1.27-2.41 and for T2DM alone 1.36, 95% CI: 1.17-1.58 (**Figure 11**). Here I have performed an up to date systematic review of the literature examining the association between T2DM and ADT.

Evidence Acquisition

The systematic review was performed in accordance with the PRISMA guidelines (94) with search terms, inclusion and exclusion criteria all defined a priori.

Search Strategy

A computerised literature search of Pubmed to identify full text and abstracts published was performed. The search was done with and without MESH terms (androgen, androgens, deprivation, therapy, therapeutics, diabetes, and diabetes mellitus). All references of the selected articles were checked, including hand searches.

Study Eligibility

The final articles were chosen based on the following set of inclusion criteria:

- Original article
- Examined the association of ADT with the risk of developing T2DM
- English language article

Excluded if:

- Review or meta-analysis
- Examined elements of the metabolic syndrome which did not include T2DM (i.e. hyperglycaemia only)

Initially, titles were reviewed to assess whether they met inclusion criteria. If, after assessing the abstract, there was any doubt regarding whether it met the relevant criteria, it was kept for more thorough, subsequent assessment. The list of potential articles was further shortened by performing detailed evaluations of the methods and results of each remaining paper. **Figure 12** provides more detailed information regarding the exclusion process. The strength of each study was assessed using the STROBE criteria (95) and is presented in **Figure 13.**

Data collection

The following details were recorded for each study: author, year of publication, country where study was undertaken, study design, number of patients, type of ADT, outcome reported and variables adjusted for in the analysis.

Evidence synthesis

The literature search identified a total of 200 studies of which 10 were deemed as initially relevant and a further one study was identified using hand searches. Using the above inclusions and exclusion criteria, four were excluded (**Figure 12**). The reasons for exclusion were: outcomes not T2DM (2) and no control group not on ADT (2). Seven studies were included in the systematic review (**Table 9**).

All seven studies were cohort studies. Five were from North American cohorts (88, 132-134, 138), one European (139) and one Asian (140). The studies combined include 97,893 men on ADT and 287,312 not on ADT. They all report an increased risk of T2DM in those men receiving ADT compared to those men that are not, particularly in those receiving GNRH agonists. The magnitude of this risk varies from a 16% increase reported by Alibhai *et al* (132) to 61% (138, 139). The one outlier is the study by *Teoh et al* (140) which reports a much higher increased risk,

HR: 3.34 (95% CI: 1.19-9.39). However, this is a much smaller study in comparison with just a few hundred patients compared to the other cohorts which include several thousand patients. This is reflected in the wide confidence intervals that they present and as such should be probably regarded as an over estimate of the potential risk. However, this is a much smaller study in comparison with just a few hundred patients compared to the other cohorts which include several thousand patients. This is reflected in the wide confidence intervals surrounding the HR that they present.

Most of the studies in this systematic review included data only on GnRH agonists and orchidectomy or combined all forms of ADT. Only two studies examine anti-androgens (AA) separately (134, 139) and both report no increased risk with those receiving AA alone.

The impact of the duration for which ADT was received and T2DM risk had been examined in two studies (88, 132) but with a relatively short exposure time (25 months). My study, presented in Chapter IV, examined in greater detail the impact of duration of ADT on risk of T2DM, with exposure times of up to greater than 10 years (139). It showed that the peak risk of T2DM in men receiving GnRH agonists/orchiectomy was within the first three years of exposure (i.e.1-1.5 years HR: 1.61, 95%CI: 1.36-1.91), before the risk tailed off with continued exposure. Thereby showing that the duration of ADT is also important with regards the risk of T2DM.

Discussion

There is good concordance between all studies examining the risk of T2DM with ADT, with all showing an increased risk. The large North American cohort studies which led to the FDA requiring a risk label on all GnRH agonists for increased risk of T2DM back in 2010 have since been corroborated by further studies in both European (139) and Asian populations (140). Additionally the literature demonstrates that both the type and duration of the ADT are important in the risk of T2DM and should be considered by physicians prescribing ADT. The biological mechanisms behind this increased risk are considered in Chapter IV.

Conclusion

The literature consistently reports that ADT increases the risk of T2DM and furthermore that the type and duration of that ADT is important in determining that risk.

Figure 11: Forest Plot for association between ADT and risk of diabetes (137)

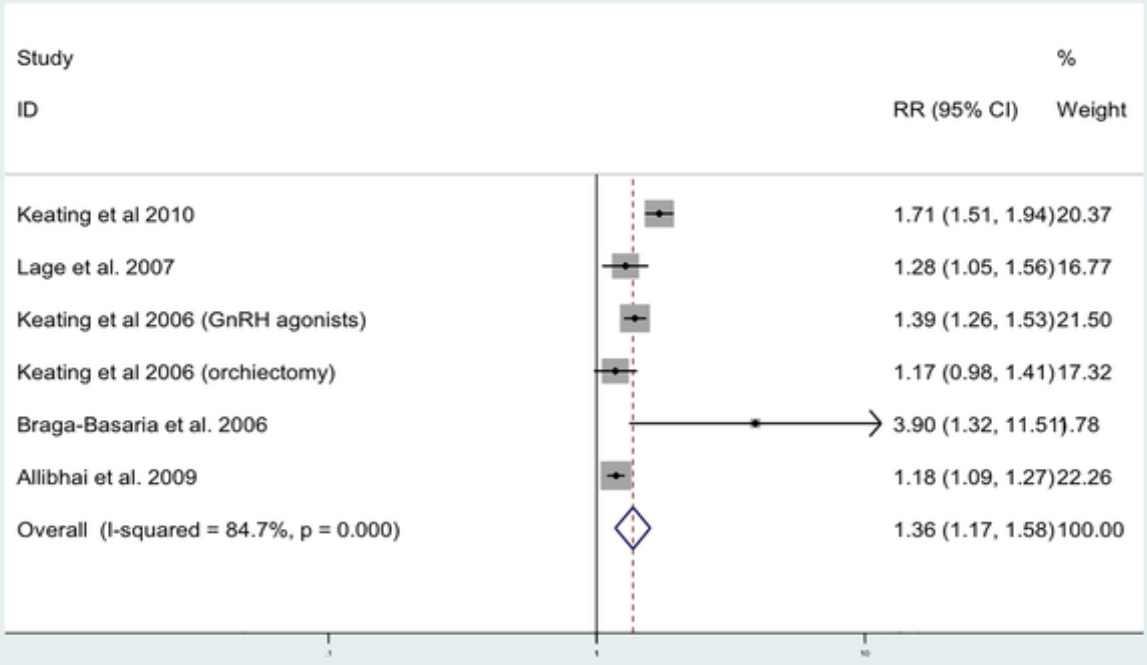
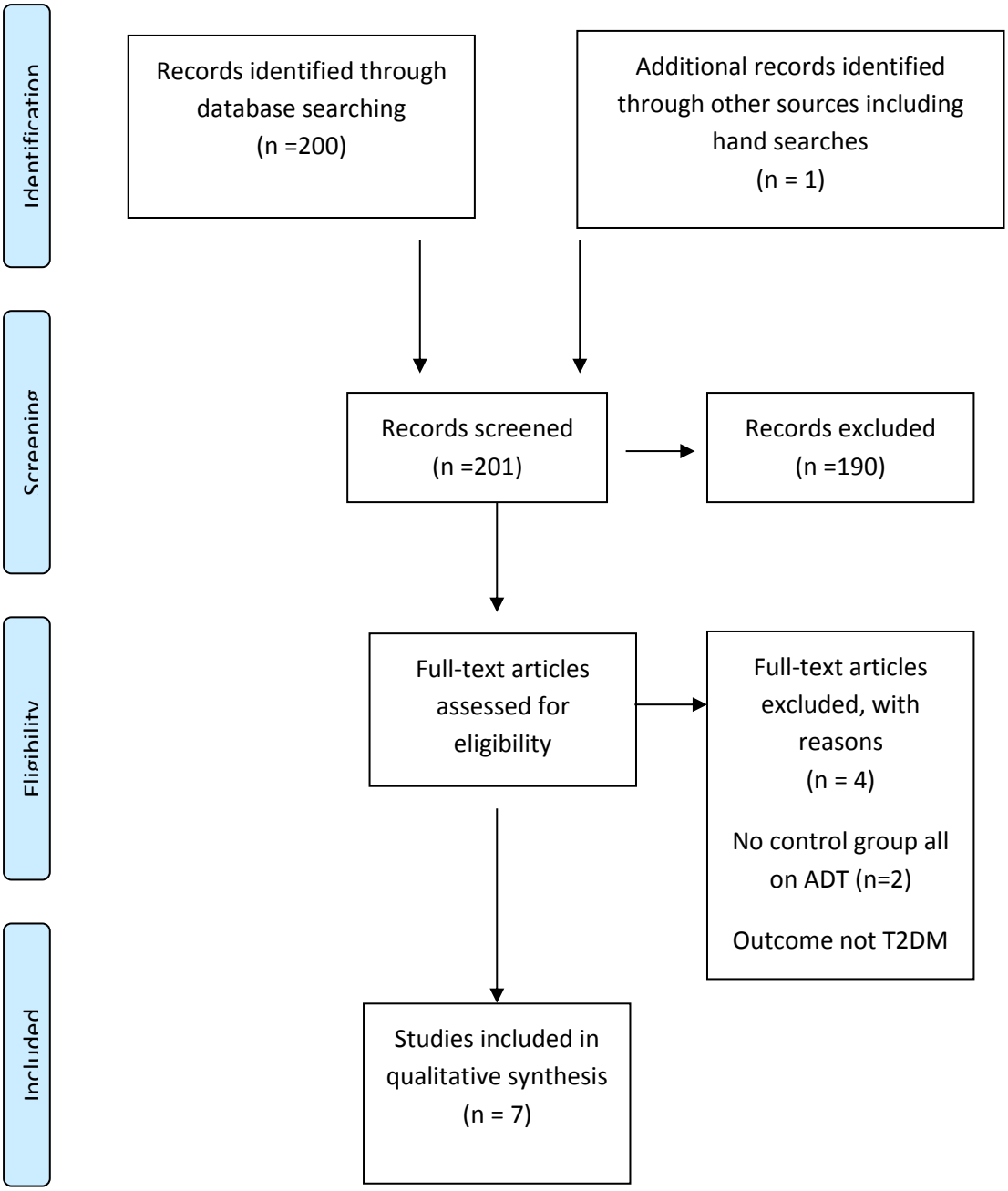


Figure 12: Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) flow diagram of article identification, screening, eligibility and inclusion for systematic review on ADT and risk of T2DM



Author, Year, Country	Study Design	No of patients	ADT Type	Main Findings	Adjusted for
Crawley D, 2016, Sweden	Prospective Cohort	34031 ADT vs. 167,205 No ADT	AA, GNRH agonists, Orch	Increased risk GnRH agonists vs. PCa free men HR 1.61 (95%CI: 1.36 - 1.91) No increased risk AA HR 0.74 (95%CI: 0.65 - 0.84).	CCI, PCa risk category , education status
Tsai HT, 2015, USA	Retrospective Cohort	2648 ADT vs. 9543 No ADT	GNRH agonist +/- AA	Increased risk with ADT vs. No ADT HR 1.61 (95% CI 1.38-1.88)	Age, race, ethnicity, year of diagnosis, cancer sequence, health plan
Teoh JY, 2015, Asia	Retrospective Cohort	219 ADT vs. 169 No ADT	GNRH agonist, Orch	Increased risk GnRH agonist HR 3.34 (95% CI 1.19-9.39) Orchiectomy HR 6.49 (95% CI 1.48-28.55) vs. No ADT	Age, T Stage, Gleason score, hypertension, dyslipidaemia, ischaemic heart disease, stroke, follow up time, type of ADT, duration of ADT
Keating NL, 2010, USA	Retrospective Cohort	14,597 ADT vs. 37,443 No ADT	AA, GNRH agonists, CAB, Orch	Increased risk with GnRH agonist vs No ADT 1.28 (95% CI 1.19 - 1.38) No increased risk with AA HR 1.02 (95% CI 0.72-1.45)	Age, race, ethnicity, year of diagnosis, marital status, socioeconomic status, Pca stage and grade, primary treatment, PSA at diagnosis, co morbidities, statin use, finasteride use
Alibhai SM, 2009, Canada	Retrospective Cohort	19, 076 ADT vs. 19076 No ADT	LHRH agonists, AA, CAB	Increased risk HR 1.16 (95%CI: 1.11–1.21)	Income and rurality
Lage MJ, 2007, USA	Retrospective Claims cohort	1231 ADT vs. 7250 No ADT	Any ADT	Increased risk with ADT HR 1.36 (95% CI 1.07-1.74)	Demographic factors, co morbid conditions, prior statin use
Keating NL, 2006, USA	Retrospective Cohort	26,570 ADT vs. 46,626 No ADT	GNRH agonist , Orch	GnRH agonists HR 1.44 (95% CI 1.34-1.55) Vs. No ADT Orch HR 1.34 (95% CI 1.20-1.50) Vs. No ADT	age, race, Hispanic ethnicity, marital status, residence, SEER region, income and education, tumor grade, comorbidity score, year of diagnosis, primary surgical therapy, prevalent coronary heart disease

Table 9: Characteristics of the 7 Studies included in the systematic review on ADT and T2DM

Figure 13: Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) checklist for observational studies included in the systematic review of ADT and T2DM.

	Item No	Recommendation	Keating 2006	Lage 2007	Alibhai 2009	Keating 2010	Teoh 2015	Tsai 2015	Crawley 2016
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	☒	☒	☒	☒	☐	☒	☒
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	☒	☒	☒	☒	☒	☒	☒
Introduction									
Background/ rationale	2	Explain the scientific background and rationale for the investigation being reported	☒	☒	☒	☒	☒	☒	☒
Objectives	3	State specific objectives, including any pre specified hypotheses	☒	☒	☒	☒	☒	☒	☒
Methods									
Study design	4	Present key elements of study design early in the paper	☒	☒	☒	☒	☒	☒	☒
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	☒	☒	☒	☒	☐	☒	☒
Participants	6	(*a*) *Cohort study*—Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up	☒	☒	☒	☒	☐	☒	☒
		Case-control study—Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls	*n/a*	*n/a*	*n/a*	*n/a*	*n/a*	*n/a*	*n/a*
		(*b*) *Cohort study*—For matched studies, give matching criteria and number of exposed and unexposed	☒	☒	☒	☒	☐	☒	☒
		Case-control study—For matched studies, give matching criteria and the number of controls per case	*n/a*	*n/a*	*n/a*	*n/a*	*n/a*	*n/a*	*n/a*

Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	☒	☒	☒	☒	☐	☒	☒
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	☒	☒	☒	☒	☒	☒	☒
Bias	9	Describe any efforts to address potential sources of bias	☒	☒	☒	☒	☒	☒	☒
Study size	10	Explain how the study size was arrived at	☐	☒	☐	☐	☐	☒	☐
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	*n/a*	*n/a*	*n/a*	☒	☒	*n/a*	*n/a*
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	☒	☒	☒	☒	☒	☒	☒
		(*b*) Describe any methods used to examine subgroups and interactions	☒	☐	☒	☒	☐	☒	☒
		(*c*) Explain how missing data were addressed	☐	☐	☐	☒	☐	☐	☐
		(*d*) *Cohort study*—If applicable, explain how loss to follow-up was addressed	☐	☐	☒	☐	☐	☒	☐
		Case-control study—If applicable, explain how matching of cases and controls was addressed	*n/a*	*n/a*	*n/a*	*n/a*	*n/a*	*n/a*	*n/a*

		(*e*) Describe any sensitivity analyses	☒	☒	☒	☒	☐	☒	☒
Results									
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	☒	☒	☒	☒	☐	☒	☒
		(b) Give reasons for non-participation at each stage	☐	☐	☒	☐	☐	☐	☐
		(c) Consider use of a flow diagram	☐	☐	☒	☐	☐	☒	☐
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	☒	☒	☒	☒	☒	☒	☒
		(b) Indicate number of participants with missing data for each variable of interest	☒	☐	☐	☒	☐	☐	☒
		(c) *Cohort study*—Summarise follow-up time (eg, average and total amount)	☒	☐	☒	☒	☒	☒	☒
Outcome data	15*	*Cohort study*—Report numbers of outcome events or summary measures over time	☒	☐	☐	☒	☒	☒	☒
		Case-control study—Report numbers in each exposure category, or summary measures of exposure	*n/a*	*n/a*	*n/a*	*n/a*	*n/a*	*n/a*	*n/a*
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	☐	☐	☐	☐	☐	☐	☒

		(*b*) Report category boundaries when continuous variables were categorized	*n/a*	*n/a*	*n/a*	*n/a*	*n/a*	*n/a*	*n/a*
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	☒	☐	☐	☒	☐	☒	☒
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	☒	☒	☒	☒	☐	☒	☒
Discussion									
Key results	18	Summarise key results with reference to study objectives	☒	☒	☒	☒	☒	☒	☒
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	☒	☒	☒	☒	☒	☒	☒
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	☒	☒	☒	☒	☒	☒	☒
Generalisability	21	Discuss the generalisability (external validity) of the study results	☒	☒	☒	☒	☐	☒	☐
Other information									
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	☒	☒	☒	☒	☒	☒	☒

Impact of T2DM treatments on PCa: Metformin and PCa

Introduction

Metformin (1,1-dimethylbiguanide hydrochloride) is a biguanide class of OHA and is commonly used for the treatment of T2DM. As described in Chapter II, metformin inhibits gluconeogenesis and reduces circulating levels of insulin (68). It is also thought to play a role in lowering triglyceride and LDL cholesterol levels (141). In addition to its anti-diabetic effect, metformin has also been associated with a reduced risk of various cancers including PCa (142-144). The literature has reported inconsistent results and several meta-analysis have been undertaken in attempt to clarify results (145-148). These are summarised below.

Existing Literature: Metformin and PCa risk

In 2015 Deng *et al.* (147) reported a decrease in risk of PCa with metformin in a meta-analysis which included seven studies (RR: 0.88, 95%CI: 0.78-0.99). Conversely in the same year, Wu *et al.* (145) included six cohort and four case-control studies in a meta-analyses and reported no association with PCa risk (RR: 0.92, 95%CI: 0.84-1.02). However, when only cohort studies were considered, a small but statistically significant reduction in risk was reported (RR: 0.92, 95%CI: 0.87-0.96). Similarly in a larger meta-analysis by Gandini *et al.* in 2014 (144) metformin treatment and PCa risk did not show any association in 12 studies (SRR: 1.06, 95%CI: 0.80-1.41), though a small but statistically significant association was seen when considering just the six prospective studies (SRR: 0.93, 95%CI: 0.89-0.97).

Existing Literature: Metformin and PCa mortality and outcomes

The meta-analysis by Deng *et al*. (147) described above also examined how metformin exposure was associated with all-cause mortality (three studies) and BCR of PCa (four studies). They reported that metformin exposure was not associated with either all-cause mortality (RR: 1.07, 95%CI: 0.86-1.32) or BCR (RR: 0.90, 95%CI: 0.75-1.09). Also in 2015 Raval *et al*. (148) published a systematic review and meta-analysis of the impact of metformin exposure on clinical outcomes in PCa. They also report no association with all-cause mortality and PCa specific mortality, but reported a marginal association with reduced risk of BCR in five studies (HR: 0.59, 95%CI: 0.67-1.01). In a further meta-analysis by Stopsack *et al.* (146) in 2016, including nine retrospective cohort studies of 9,186 patients, no overall association with PCa specific mortality was seen, but metformin exposure was associated with improved OS in these studies (HR: 0.88, 95%CI: 0.86-0.90) and with a decreased risk of BCR (HR: 0.79, 95%CI: 0.63-1.00).

Evidence Acquisition

As several full meta-analyses and systematic reviews were published in 2015/2016, a full systematic review of the literature was not deemed valuable. However, I reviewed the literature since 2015 searching Pubmed using terms (with and without MESH terms): metformin, prostate cancer, risk, mortality and outcomes. Two additional studies were identified (149, 150).

Evidence Synthesis

The two new studies identified are summarised in **Table 10.** Both were large Scandinavian cohort studies. Haggstrom et al (149) reported that men with more than one year duration of T2DM had a reduced PCa risk, but that those receiving metformin specifically did not (HR: 0.96, 95%CI: 0.77-1.19). Conversely, the Finnish study by Haring *et al*. (150) reported that men using antidiabetic drugs had lowered overall PCa risk (HR: 0.85, 95%CI: 0.79–0.92) and among antidiabetic drug users, metformin decreased overall PCa risk (HR: 0.81, 95%CI: 0.69–0.95) in a dose-dependent manner.

Discussion

Despite many studies examining the impact of metformin on PCa risk and outcomes they continue to offer conflicting results. This may be explained by the wide heterogeneity in the design and quality of these studies. Much of the literature fails to take into account some important potential sources of bias including detection bias, immortal time bias, exposure definition and sufficient baseline adjustment. Many studies do not consider that treatment with metformin changes through time. It is also associated with disease severity, and as T2DM severity may be on the causal pathway with PCa risk or mortality, it can be said to be a time dependent confounder. Standard statistical methods used in much of the literature are not able to estimate potential effects correctly controlling for time –dependent confounders (151).The meta-analyses performed to provide clarity, have also provided conflicting results. In their meta-analysis Stopsack *et al.* (146) attempted to take into account the differing designs and quality of the literature. In their primary analysis, they only included studies with a clear risk window and in a secondary analysis examined those studies with potential immortal time bias. They showed that an otherwise modest association with reduced PCa risk was magnified in the studies with potential immortal time bias (HR: 0.52, 95%CI: 0.41-0.65). This highlights the need to take into account the quality of studies when performing meta-analysis. Two well designed and well powered Canadian studies by Margel *et*

al. (143, 152) reported that an increased cumulative duration of metformin exposure after PCa diagnosis was associated with decreases in both all-cause and PCa-specific mortality among diabetic men, but was not associated with PCa incidence. The biological mechanisms underlying these potential associations are reviewed in Chapter VI.

Conclusion

The current epidemiological evidence shows neither a conclusive decrease in risk of PCa risk or improvement in PCa or all-cause mortality with metformin. Further rigorous, well designed and powered studies are needed to clarify these potential associations.

Table 10: Two additional studies identified in systematic review of metformin and PCa risk and outcomes

Author, Year, Country	Study Design	No of patients	Main Findings	Adjusted for
Haring, Finland ,2017	Cohort	78,615	Metformin decreased PCa incidence in a dose dependent manner (HR 0.81, 95% CI 0.69–0.95)	Age, trial arm, medications
Haggstrom, Sweden, 2017	Cohort	612,846	Metformin did not decrease PCa incidence (HR 0.96 95%CI 0.77-1.19)	Age, education, CCI, county

Impact of PCa on T2DM control and treatments

Introduction

The relationship between PCa and T2DM has been extensively studied with respect to the effects of T2DM on PCa risk and progression, as described above. However, conversely the impact of a PCa diagnosis on the treatment of T2DM has received less attention. In this final section, I will consider the impact of PCa on T2DM control and treatments. In particular PCa treatments including ADT and corticosteroids given alongside chemotherapy may have an impact on the management of pre-existing T2DM. However, there is little literature in this area. A systematic review of the published works on this subject is detailed below.

Evidence Acquisition

The systematic review was performed in accordance with the PRISMA guidelines (94) with search terms, inclusion and exclusion criteria all defined a priori.

Search Strategy

A computerised literature search of Pubmed to identify full text and abstracts published was performed. The search was done with and without MESH terms (prostate cancer, diabetes control). All references of the selected articles were checked, including hand searches.

Study Eligibility

The final articles were chosen based on the following set of inclusion criteria:

- Original epidemiological study
- Examined the impact of PCa diagnosis or treatment on T2DM control or treatment
- English language article

The studies were excluded if:

- Review or meta-analysis

Initially, titles were reviewed to assess whether they met inclusion criteria. If, after assessing the abstract, there was any doubt regarding whether it met the relevant criteria, it was kept for more thorough, subsequent assessment. The list of potential articles was further shortened by performing detailed evaluations of the methods and results of each remaining paper. **Figure 14** provides more detailed information

regarding the exclusion process. The strength of each study was assessed using the STROBE criteria (95) and is presented in **Figure 15**.

Data collection

The following details were recorded for each study: author, year of publication, country where study was undertaken, study design, number of patients, main outcome and main findings.

Evidence Synthesis

The literature search identified a total of 200 studies of which 30 were initially relevant. Using the above inclusions and exclusion criteria, 27 were excluded (**Figure 14**). The reasons for exclusion were: review or meta-analysis (n=13), outcome not T2DM controls or treatment change (n=12), not PCa specific (n=1), RCT (n=1). Three studies were eventually included in the systematic review (**Table 11**).

All three studies identified were North American cohort studies (153-155). By far the largest of these studies by Keating *et al*. (153) included 2,237 pairs of propensity matched men with PCa and T2DM who did or did not receive ADT. They calculated mean HbA1c at baseline for both the ADT and No ADT groups and then examined the difference in difference at baseline, one and two years between the groups. They reported that HbA1c increased at one year for men treated with ADT to 7.38% and decreased among men not treated with ADT to 7.14%, for a difference in differences of +0.24 (P=0.008). Results were similar at two years (P=0.03). They also performed Cox proportional hazards regression model in the propensity matched data to assess if ADT was associated with initiating or adding a new class of anti-diabetes drug. They reported an increased risk of initiating an additional anti-diabetic medication in those men on ADT (HR: 1.20, 95%CI: 1.09-1.32), despite the rise in HbA1c seen in those receiving ADT.

Derweesh *et al.* (154) also examined glycaemic control in men with pre-existing T2DM starting on ADT. Glycaemic control was defined by comparing mean fasting blood glucose (FBG) and HbA1c levels before and after ADT for comparison. Subsets were then analysed to determine the percentage of patients with a ≥10% rise in mean FBG or mean HbA1c after starting ADT. They reported an increase of ≥10% in serum HbA1c in 15 patients (19.5%) and an increase of ≥10% in FBG in 22 patients (28.6%). However, there was no comparison group in this study.

The final study identified in this systematic review is a descriptive cohort study of 30 patients with T2DM and genitourinary cancer, 26 of whom had PCa, who were receiving corticosteroids alongside their chemotherapy (155). They examined changes in T2DM treatment and hospitalisations due to hyperglycaemia and reported that 40% of patients required a change in their T2DM management (n=4) and 20% (n=2) required hospitalizations for hyperglycaemia.

Discussion

This systematic review has highlighted a gap in the existing literature examining the impact of PCa and its treatments on the control and management of pre-existing T2DM. The studies published and described above all suggest that PCa treatments, including ADT and corticosteroids, do impact the management of pre-existing T2DM. In light of the recent change to use of up front chemotherapy, alongside ADT, for patients presenting with metastatic disease at presentation, during which steroids are given routinely, this will become increasingly clinically important. However, the existing studies are very limited. There is a need for further original research into this area. In Chapter IV of this thesis I aimed to explore the impact of PCa diagnosis on existing T2DM treatment in more detail using data from PCBaSe.

Figure 14: Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) flow diagram of article identification, screening, eligibility and inclusion for systematic review on impact of PCa on T2DM control and treatment

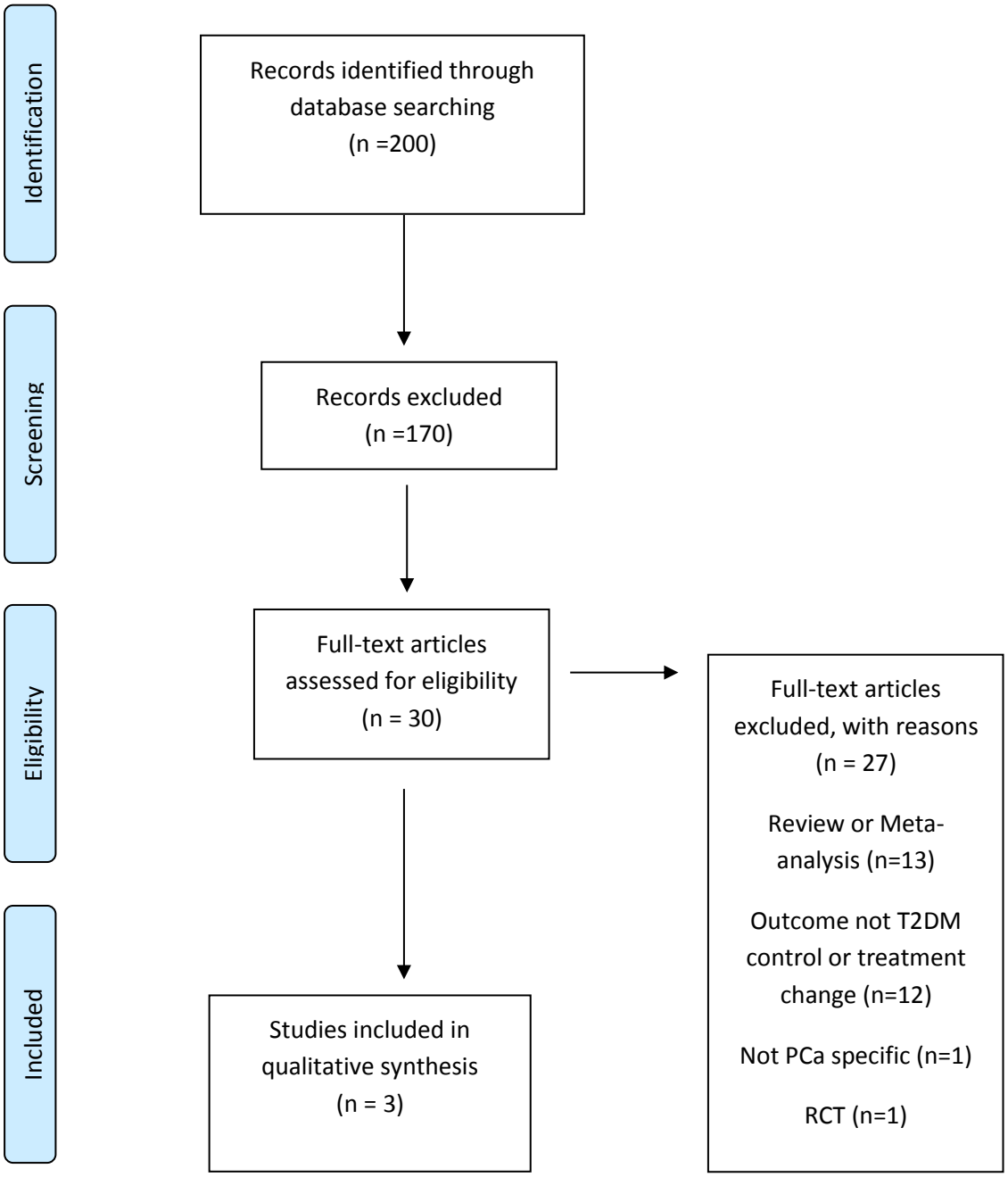


Table 11: Characteristics of studies included in the systematic review on impact of PCa on T2DM control and treatments

Author, Year, Country	Study Design	No of patients	Main Outcomes	Main Findings
Keating, 2014, USA	Cohort with propensity matching	2237 pairs of propensity matched men with PCa and T2DM who were or were not treated with ADT	The effect of ADT onT2DM control, as measured by HbA1c levels and the intensification of T2DM drug therapy.	HbA1c increased at 1 year for men treated with ADT (7.38 from 7.24 p value 0.04) Receipt of ADT was also associated with an increased risk of addition of T2DM medication (HR 1.20 95% CI: 1.09-1.32)
Rowbottom, 2015, Canada	Cohort	30 GU Cancer patients: 26 PCa 4Bladder Ca	Change in T2DM management or hospitalisation due to T2DM in those receiving corticosteroids with chemotherapy	40% required a change in their diabetes management (n=4) 20% (n=2) required hospitalizations
Derweesh, 2007,USA	Cohort	77 patients	To assess worsening glycaemic control in men with established T2DM after starting ADT for PCa	An increase of≥10% in serum HbA1c in 15 patients (19.5%) An increase of ≥10% in FBG in 22 patients (28.6%)

Figure 15: Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) checklist for observational studies included in the systematic review of ADT and T2DM

	Item No	Recommendation	Rowbottom 2015	Keating 2014	Derweesh 2007
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	☒	☒	☒
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	☒	☒	☒
Introduction					
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	☒	☒	☒
Objectives	3	State specific objectives, including any pre specified hypotheses	☒	☒	☒
Methods					
Study design	4	Present key elements of study design early in the paper	☒	☒	☒
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	☒	☒	☒
Participants	6	(*a*) *Cohort study*—Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up	☐	☒	☒
		Case-control study—Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls	*n/a*	*n/a*	*n/a*
		(*b*) *Cohort study*—For matched studies, give matching criteria and number of exposed and unexposed	☐	☒	☐
		Case-control study—For matched studies, give matching criteria and the number of controls per case	*n/a*	*n/a*	*n/a*
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	☐	☒	☒

Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	☐	☒	☒
Bias	9	Describe any efforts to address potential sources of bias	☐	☒	☐
Study size	10	Explain how the study size was arrived at	☐	☒	☐
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	*n/a*	*n/a*	*n/a*
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	☐	☒	☒
		(*b*) Describe any methods used to examine subgroups and interactions	☐	☒	☐
		(*c*) Explain how missing data were addressed	☐	☐	☐
		(*d*) *Cohort study*—If applicable, explain how loss to follow-up was addressed	☐	☒	☐
		Case-control study—If applicable, explain how matching of cases and controls was addressed	*n/a*	*n/a*	*n/a*
		(*e*) Describe any sensitivity analyses	☐	☒	☐
Results					

Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	☒	☒	☒
		(b) Give reasons for non-participation at each stage	☐	☐	☐
		(c) Consider use of a flow diagram	☐	☐	☐
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	☒	☒	☒
		(b) Indicate number of participants with missing data for each variable of interest	☐	☒	☐
		(c) *Cohort study*—Summarise follow-up time (eg, average and total amount)	☐	☒	☒
Outcome data	15*	*Cohort study*—Report numbers of outcome events or summary measures over time	☒	☒	☒
		Case-control study—Report numbers in each exposure category, or summary measures of exposure	*n/a*	*n/a*	*n/a*
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	☐	☒	☐
		(*b*) Report category boundaries when continuous variables were categorized	*n/a*	*n/a*	*n/a*

		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	☐	☒	☐
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	☐	☒	☐
Discussion					
Key results	18	Summarise key results with reference to study objectives	☒	☒	☒
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	☒	☒	☒
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	☒	☒	☒
Generalisability	21	Discuss the generalisability (external validity) of the study results	☐	☒	☒
Other information					
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	☒	☒	☐

Conclusion

This chapter begun with a systematic review of the impact of pre-existing T2DM on PCa incidence and corroborates previously published findings, indicating that T2DM has a protective effect on PCa risk. Several potential biological mechanisms and possible biases to explain this inverse association were discussed. Secondly the impact of pre-existing T2DM on stage and grade was explored. Some studies have suggested that the inverse association is seen only in low risk cancers and that those with T2DM are actually more likely to have higher grade and stage PCa. However, this is not consistent with existing meta-analysis and at present no conclusion can be drawn on the impact of T2DM on risk of PCa of different grades and stages. The existing literature suggests that T2DM may be associated with increased risk of all-cause and PCa-specific mortality, but the existing literature has some significant limitations. The relationship between T2DM and PCa is further complicated by the interaction between the two conditions and their treatments. In this chapter, the relationship between ADT and T2DM was examined and there is good concordance between all studies, with all showing an increased risk of T2DM. The epidemiological evidence examining the relationship between metformin and PCa, however, is less convincing. It shows neither a conclusive decrease in risk of PCa risk nor an improvement in PCa or all-cause mortality with metformin exposure. Finally, in this chapter I have highlighted a gap in the existing literature examining the impact of PCa and its treatments on the control and management of pre-existing T2DM. Hence in Chapter IV of this thesis I aimed to explore the impact of PCa diagnosis on existing T2DM treatment in more detail using data from PCBaSe.

Chapter IV: PCBaSe

Introduction

As highlighted in Chapter III, the interplay between T2DM and PCa is complex. Several gaps and weaknesses in the literature were highlighted by the systematic reviews. These included:

- The impact of pre-existing T2DM on PCa outcomes and mortality
- The impact of a PCa diagnosis on the management and control of pre-existing T2DM
- The impact of type and duration of ADT on the risk of T2DM

In this chapter, using data from PCBaSe I aimed to further examine these important elements of the relationship between PCa and T2DM.

PCBaSe and other national Swedish registries

The first regional PCa register was established in the South-East health care region of Sweden in January 1987. In the early 1990's similar registers were established in further regions. These separate registers amalgamated to form the National Prostate Cancer Register (NPCR) of Sweden in 1996. Law mandates that all newly biopsy-confirmed PCa cases have to be registered (156). Firstly, each new case is reported to the regional cancer register where data are validated and checked for completeness, before being entered into the online IT platform for the NPCR, the Information Network for Cancer care (INCA) (157).

NPCR includes information on date of diagnosis, age at diagnosis, tumour stage and differentiation and serum levels of PSA at time of diagnosis. PCa risk categories are determined according to a modified version of the National Comprehensive Cancer Network Guideline (39):

- Low risk: local clinical stage T1-2, Gleason score of 2-6 and PSA< 10 ng/ml
- Intermediate risk: T1-2, Gleason score 7 and/or PSA 10-20 ng/ml
- High risk: T3 and/or Gleason score 8-10 and/or PSA 20—50 ng/ml
- Regionally metastatic/locally advanced: T4 and/or N1 and/or PSA 50-100 ng/ml in the absence of distant metastases (M0 or MX)
- Distant metastases: M1 and/or PSA > 100 ng/ml

PCBaSe Sweden 2.0 is based on the NPCR of Sweden, which became fully nationwide in 1998 and covers 98% of all newly diagnosed cases of PCa, as

compared to the Swedish Cancer Register (**Figure 16**) (120, 156, 158). Using the Swedish personal identity number, five PCa-free men from the general population in Sweden were randomly selected within sets of men who matched the index case on birth year and county of residence and were included in a PCa-free comparison cohort (156). Both men with PCa and those in the comparison cohort were subsequently linked to a series of national health care registers and demographic databases, to obtain data on comorbidity, socioeconomic status, and cause of death (**Table 12**). The aim was to create a database with extensive longitudinal data for a population-based nationwide cohort in men with PCa. Subsequent versions including PCBaSe 2.1, 2.2 and 3.0 were created with increasing follow up times.

A further database PCBaSe^{traject} was then created to capture information on the treatment trajectory of individual patients (120). It focuses specifically on men diagnosed with PCa between 1992 and 2012, with complete data on treatment trajectory (**Figure 17**). It includes all data in PCBaSe 3.0, but has additional linkages to allow treatment actually received, rather than just treatment planned, to be captured. This includes data from RetroRad, a retrospective data collection/ verification from oncology information systems and local databases of radiotherapy departments. Data collected/verified included type, total dose and fractionation of the radiotherapy received. This was necessary as prior to 2008 very little information regarding radiotherapy was captured.

As mentioned above PCBaSe is linked to a series of national health care registers and demographic databases, to obtain data on comorbidity, socioeconomic status, and cause of death (**Table 12**). The Swedish Cancer Register begun in 1958. Both the clinician and the pathologist/cytologist recording the cancer are responsible for reporting the case. The linkage to the personal identity numbers, ensures no duplicates are recorded. A registrable cancer is one which is confirmed histologically or cytologically, or when diagnosed by a clinician based on other diagnostic tests (159). The patient register includes diagnostic codes for conditions in both the inpatient and outpatient setting (156). The Swedish Cause of Death Register has existed since 1953 and uses the tenth version of the International Classification of Diseases (ICD-10) to capture cause of death data for all persons who were registered in Sweden at time of death, regardless of whether the death occurred inside or outside of the country (160). There are also linkages to the Registers of Total population and Changes and Immigration and Emigration as well

as the Swedish Household Census (**Table 12**). The Longitudinal database on socioeconomic factors (LISA) is collected by Statistics Sweden and is a comprehensive socioeconomic database which is updated annually (161). The Prescribed Drug Register began on 1st July 2005 and captures all prescribed across Sweden (162). The Swedish National Diabetes Register (NDR) began in 1996 in response to the Saint Vincent declaration, which called for tools to provide continuous quality assurance in the care of people with T2DM. It covers all Swedish patients with type 1 or T2DM over the age of 18 years. Data collected includes baseline demographics, risk factors, medications and complications. Currently, over 90% of hospitals and clinics record their data via an online portal (www.ndr.nu) meaning that the vast majority of patients with T2DM are included. However, historically coverage was not as wide ranging, particularly in older patients or those with multiple co-morbidities (163). Due to this in the first and third study presented in this chapter the prescribed drug register is used to define diabetes based on drug prescribing rather than the NDR. As a result only those receiving pharmacological treatment for T2DM are captured. This potential bias is further explored in the discussion sections for those studies.

Figure 16: The six regions in Sweden registering information on prostate cancer diagnoses for the NPCR and the year the registration was introduced (156)

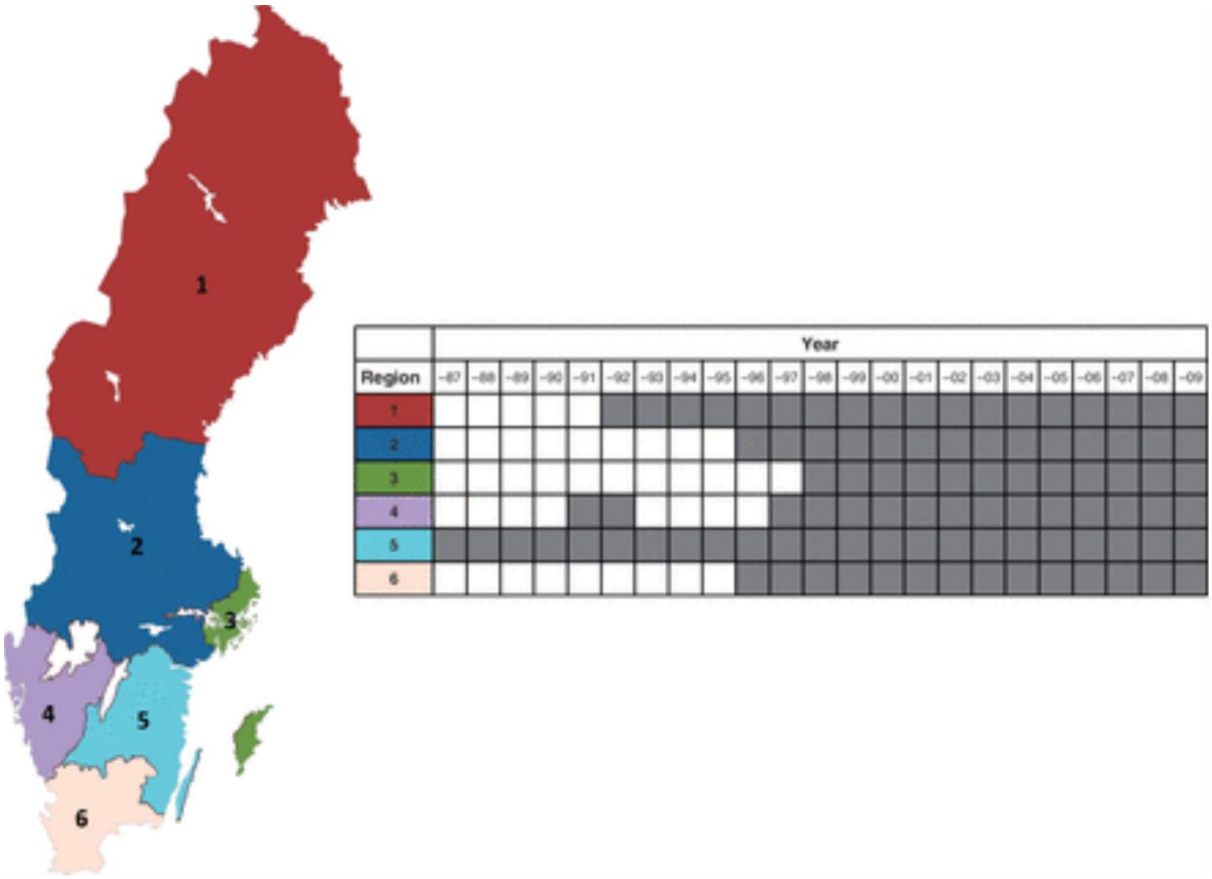
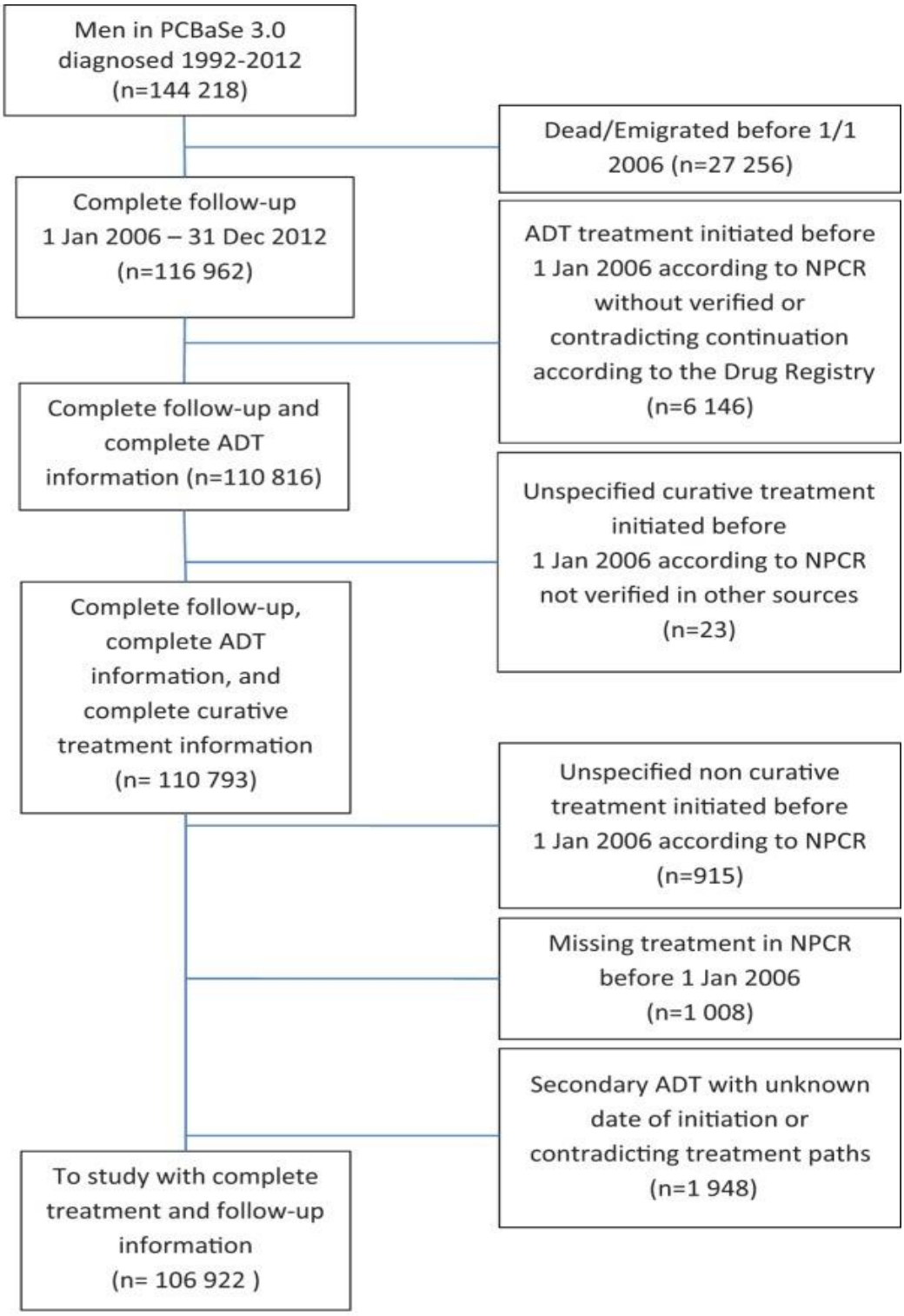


Table 12: Registers queried for information on subjects in PCBaSe by linkage to the NPCR of Sweden and their comparison cohort.

Register	Data Content
Swedish Cancer Register	Notification of cancer diagnosis, site and date. Reporting mandated by law from clinician and pathology department
Patient Register	In-patient and Out-patient Registers, with diagnostic and surgical codes
Cause of Death Register	Date and underlying and contributing causes of death coded according to ICD-10
Register of the Total Population and Changes	PIN for all Swedish residents, country of birth, marital status
Registers of Immigration and Emigration	Date of immigration and emigration
Sweden Household Census	Demographics collected 1960–90 including e.g. profession
Longitudinal database on socioeconomic factors (LISA)	Extensive set of socio-economic factors with annual update including marital status, profession.
The Prescribed Drug Register	All prescribed and dispensed drugs for all Swedish residents since July 2005
National Diabetes Register	Details on diabetes diagnosis and metabolic factors for adults with diabetes in Sweden

Figure 17: Flow Chart of patient selection for PCBaSe [traject] (120).



NPCR: National Prostate Cancer Register, ADT: androgen deprivation therapy.

Association between Type 2 diabetes, curative treatment and survival in men with intermediate and high risk localised prostate cancer

This study has been presented as an oral and poster presentation at EAU London 2017, where it won best poster in session (**Appendix 1**). It was subsequently published in the British Journal of Urology International in April 2017 (164) (**Appendix 1**).

Rationale

As discussed in Chapters II and III, PCa and T2DM are both increasing prevalent conditions and as a result often occur concurrently in the same patients. Existing literature does not fully explore the impact that a pre-existing diagnosis of T2DM has on the treatment received for PCa. It is known that there is an association between comorbidities (including T2DM) and life-expectancy in men with localised PCa (165-167) and current PCa treatment guidelines recommend that a man should have a life expectancy of ten years or more in order for curative treatment to be indicated (168). However, the association between pre-existing T2DM, curative treatment and survival in men with localised PCa remains unknown. Hence, I used data from PCBaSe Sweden to investigate if a diagnosis of T2DM decreased the probability of curative treatment in men with localised PCa and how this was associated with PCa-specific and all-cause mortality.

Methods

Study population and data collection

All men diagnosed with intermediate or high risk localised PCa (i.e. eligible for radical treatment with either RP or EBRT) between 1st January 2006 and 31st December 2014 were included in the study. A six month run in period was used following the start of the Prescribed Drug Register on 1st July 2005. The Regional Research Ethics Board at Umeå University approved this study.

The main outcome variable for this study, treatment with RP and RT, was retrieved from PCBaSe^{traject}, which represents actual treatment received, not just intended primary treatment. Only primary treatment, i.e. first definitive treatment received after PCa diagnosis and not subsequent treatments were examined. The main exposure variable for this study, T2DM, was defined as receiving two or more consecutive prescriptions for an anti-diabetic drug within 6 months. Information on filled prescriptions of metformin, SU and insulin was obtained from The Prescribed

Drug Register using ATC codes (insulin- ANA, metformin- A10BA/BD, SU- A10BB) (169). Less than 2% of those with T2DM received prescriptions for alternative oral hypoglycaemics; in this analysis these were considered in the metformin group. Those with Type 1 diabetes receiving insulin prescriptions were not excluded; however, these cases were few. There were 40 patients with Type 1 diabetes in the intermediate and 22 in the high risk PCa group. Comorbidities were measured by the Charlson Co-morbidity Index (CCI), which assigns weights to a number of medical conditions, including diabetes and hypertension based on discharge diagnoses in the Patient Register (166). In this analysis, diabetes was excluded from the CCI score. Each condition was assigned a score of 1, 2, 3 or 6 and the final CCI is given as the sum of these scores. Individuals were grouped into CCI categories for final scores of 0, 1, 2 or 3+ in accordance with previous publications. Information on age at diagnosis, T-stage, Gleason score, PSA at diagnosis, proportion of cores with cancer, mode of detection of PCa, education and civil status was also used. For men with missing data on Gleason score (0.7%), multivariate imputation using chained equations (MICE), also known as imputation, was applied using fully conditional specifications (170). The MICE method imputes multiple variables sequentially using univariate fully conditional specifications.

Analysis

Multivariate logistic regression was used to calculate odds ratios for receiving curative treatment in men with and without T2DM (as defined above). The analysis was adjusted for age, T stage, Gleason score, proportion of cores with cancer, CCI (excluding diabetes), mode of detection, education and civil status. When adjusting for PSA linear splines with knots at 3, 10 and 20 were used to reflect clinically relevant cut offs.

A further analysis was performed to evaluate how an additional diagnosis of hypertension, dyslipidaemia, or CVD as compared to only T2DM affected the association between T2DM and curative treatment. ATC codes were used for the following prescriptions from the Prescribed Drug register to assess these additional diagnoses: statins (C10), anti-hypertensive (C02) and anti-coagulants (B01).

To evaluate the association of PCa and T2DM with survival, a comparison cohort including men with only T2DM from the PCa- free cohort was created. First, all index cases were selected (PCa and T2DM, as registered with a date of diagnosis from the NDR). Controls in the comparison cohort were matched with these index

cases on age (+/- 1 year), duration of T2DM and type of T2DM treatment (insulin vs. OHA). For each index case, five controls were selected. Overall survival up to eight years of follow-up was then calculated for men in the comparison cohort and for men with T2DM and PCa who did and did not receive curative treatment. 8-year survival probabilities were assessed as data was only available for the period 2006-2014. Finally, the cumulative incidence of PCa specific and death from other causes was calculated in those who did and did not receive curative treatment.
All data management was performed with SAS version 9.3 (SAS Institute, Cary, NC) and all data analysis was conducted with R version 2.13.2 (R Foundation for Statistical Computing, Wien, Austria).

Results

2,210 men with PCa and T2DM and 23,071 men with PCa only were included in the analysis. Of those with T2DM, 916 were treated with insulin and 1,537 with metformin (**Table 13**). Men with T2DM were older than those without T2DM; only 6% of men with T2DM were under 60 years, compared to 13% of men with no T2DM (**Table 13**). Men with T2DM also had higher CCI and were more likely to have high risk rather than intermediate risk prostate cancer, in comparison to men without T2DM (**Table 13**). Those with T2DM were also more likely to have a Gleason score of greater than 8, a higher proportion of cores with cancer and a PSA >20 ng/ml (**Table 13**).

Men with both T2DM and PCa were less likely to receive curative treatment for PCa than those without T2DM (OR: 0.78; 95%CI: 0.69-0.87) (**Table 14**). Men with T2DM treated with insulin were less likely to receive curative treatment (OR: 0.62; 95%CI: 0.53-0.74) than men on metformin (OR: 0.91; 95%CI: 0.80-1.04) (**Table 14**).

Men with other comorbidities (based on additional filled prescriptions for drugs for hypertension, dyslipidaemia, or CVD) in addition to T2DM had virtually the same probability of curative treatment for PCa; T2DM only (OR: 0.78; 95%CI: 0.69-0.88), T2DM and dyslipidaemia (OR: 0.79; 95%CI: 0.69-0.90), and T2DM and CVD (OR: 0.75; 95%CI: 0.60-0.93) (**Table 15**).

The 8 year OS was lower in PCa-free men with T2DM compared to men with T2DM and PCa who received curative treatment. At eight years of follow-up, the survival was 73% for men with T2DM and no PCa, 79% for men with T2DM and high risk PCa who received curative treatment and 33% for men with T2DM and high risk

PCa who did not receive curative treatment (**Figure 18**). Corresponding numbers for intermediate risk PCa were 77%, 86% and 55%. The cumulative incidence of PCa death was low in both intermediate and high risk PCa when curative treatment was received. In men with intermediate risk PCa who were not curatively treated, the cumulative incidence of PCa death remained low at 8 years whilst the cumulative incidence of death from other causes was much higher. However, in those men with high risk PCa the cumulative incidence of PCa death contributed to a much greater proportion of the overall death in those not treated curatively (**Figure 19**).

Table 13: Patient characteristics by diabetes status and diabetes treatment in Prostate Cancer database Sweden (PCBaSe) included in the study Association between Type 2 diabetes, curative treatment and survival in men with intermediate and high risk localised prostate cancer

	No diabetes	%	T2DM[1] (all)	%	Insulin	%	Metformin	%
	n= 23071		n= 2210		n= 916		n= 1537	
Age at PCa diagnosis								
	67.9		70		70.1		69.6	
Age, years								
<60	3016	13.1	134	6.1	55	6.0	94	6.1
60-64	4593	19.9	312	14.1	117	12.8	235	15.3
65-69	6184	26.8	611	27.6	266	29.0	451	29.3
70-74	5277	22.9	603	27.3	246	26.9	422	27.5
75-80	4001	17.3	550	24.9	232	25.3	335	21.8
Year of PCa diagnosis								
2006-2008	7843	34.0	672	30.4	276	30.1	441	28.7
2009-2010	8006	34.7	751	34.0	321	35.0	511	33.2
2011-2012	7222	31.3	787	35.6	319	34.8	585	38.1
CCI[2]								
0	18985	82.3	1512	68.4	558	60.9	1116	72.6
1	2428	10.5	383	17.3	183	20.0	245	15.9
2	1187	5.1	190	8.6	89	9.7	118	7.7
3+	471	2.0	125	5.7	86	9.4	58	3.8
Risk category[3]								

Table 14: Patient characteristics by diabetes status and diabetes treatment in Prostate Cancer database Sweden (PCBaSe) included in the study Association between Type 2 diabetes, curative treatment and survival in men with intermediate and high risk localised prostate cancer

Intermediate risk	14503	62.9	1187	53.7	468	51.1	825	53.7
High risk	8568	37.1	1023	46.3	448	48.9	712	46.3
Educational level								
Low	7897	34.2	919	41.6	391	42.7	631	41.1
Middle	9091	39.4	854	38.6	355	38.8	597	38.8
High	5933	25.7	417	18.9	164	17.9	295	19.2
Missing	150	0.7	20	0.9	6	0.7	14	0.9
Civil status								
Not married	7241	31.4	779	35.2	332	36.2	551	35.8
Married	15830	68.6	1431	64.8	584	63.8	986	64.2
Gleason Score								
GS 2-6	4913	21.3	387	17.5	181	19.8	261	17.0
GS 7 (3+4)	9471	41.1	802	36.3	301	32.9	561	36.5
GS 7 (4+3)	4378	19.0	458	20.7	191	20.9	307	20.0
GS 7 UNS	162	0.7	14	0.6	4	0.4	10	0.7
GS 8	2627	11.4	334	15.1	143	15.6	238	15.5
GS 9-10	1520	6.6	215	9.7	96	10.5	160	10.4
Percentage cores positive for cancer								
0-33%	8767	43.5	779	40.3	321	40.4	531	39.1
33-66%	7043	35.0	650	33.6	267	33.6	467	34.4
66-100%	4335	21.5	505	26.1	206	25.9	360	26.5
Serum PSA (ng/ml)								

Table 15: Patient characteristics by diabetes status and diabetes treatment in Prostate Cancer database Sweden (PCBaSe) included in the study Association between Type 2 diabetes, curative treatment and survival in men with intermediate and high risk localised prostate cancer

0-3	418	1.9	52	2.5	23	2.6	32	2.2
3-10	10112	46.0	909	43.0	336	38.5	661	45.1
10-20	7605	34.6	706	33.4	313	35.9	478	32.6
20-50	3837	17.5	446	21.1	201	23.0	295	20.1
Primary Treatment								
ADT[4]	3552	15.4	560	25.3	276	30.1	336	21.9
Radical Prostatectomy	9057	39.3	501	22.7	182	19.9	377	24.5
Radiotherapy	6343	27.5	687	31.1	257	28.1	524	34.1
Watchful Waiting	4119	17.9	462	20.9	201	21.9	300	19.5

[1]Type 2 Diabetes

[2]Charlson Co-morbidity Index

[3]Risk groups according to modification of the National Comprehensive Cancer Network Practice Guidelines (39)

[4] Androgen deprivation therapy

Table 16: Odds ratios and 95% confidence intervals of curative treatment by diabetes status in the study Association between Type 2 diabetes, curative treatment and survival in men with intermediate and high risk localised prostate cancer

	All men with diabetes		Insulin T2DM		Metformin T2DM	
Model						
	OR	95%CI	OR	95%CI	OR	95%CI
Diabetes	0.58	(0.53 - 0.63)	0.47	(0.41 - 0.53)	0.73	(0.66 - 0.81)
+ Age	0.73	(0.66 - 0.81)	0.55	(0.47 - 0.65)	0.87	(0.77 - 0.99)
+CCI[1]	0.78	(0.70 - 0.86)	0.62	(0.53 - 0.72)	0.91	(0.81 - 1.03)
+T Stage	0.79	(0.71 - 0.88)	0.62	(0.53 - 0.73)	0.93	(0.82 - 1.05)
+Gleason	0.75	(0.67 - 0.83)	0.60	(0.51 - 0.71)	0.88	(0.77 - 0.99)
+PSA[2]	0.75	(0.67 - 0.83)	0.61	(0.51 - 0.71)	0.88	(0.77 - 1.00)
+% positive cores	0.74	(0.66 - 0.83)	0.59	(0.50 - 0.70)	0.87	(0.77 - 0.99)
+mode of detection	0.76	(0.68 - 0.84)	0.61	(0.51 - 0.72)	0.88	(0.78 - 1.01)
+Education	0.77	(0.69 - 0.86)	0.62	(0.52 - 0.73)	0.90	(0.79 - 1.02)
+Civil Status	0.78	(0.69 - 0.87)	0.62	(0.53 - 0.74)	0.91	(0.80 - 1.04)

Crude model is followed by multivariate models with increasing number of factors included as adjustment

[1]Calculated excluding diabetes
[2]For PSA linear splines with knots at 3, 10 and 20 were used

Table 17: Odds ratios and 95% confidence intervals of curative treatment in men with diabetes and additional comorbidities compared to those with T2DM only in the study Association between Type 2 diabetes, curative treatment and survival in men with intermediate and high risk localised prostate cancer

	T2DM and hypertension[3]		T2DM and high cholesterol[3]		T2DM and CVD[3]	
Model	OR	CI	OR	CI		
Crude	0.54	(0.49 - 0.60)	0.58	(0.52 - 0.65)	0.48	(0.40 - 0.57)
Age	0.73	(0.65 - 0.81)	0.73	(0.65 - 0.83)	0.66	(0.54 - 0.81)
CCI[1]	0.79	(0.70 - 0.88)	0.80	(0.71 - 0.91)	0.79	(0.64 - 0.97)
T Stage	0.80	(0.71 - 0.90)	0.81	(0.71 - 0.93)	0.80	(0.65 - 0.98)
Gleason	0.75	(0.67 - 0.85)	0.77	(0.67 - 0.88)	0.75	(0.60 - 0.92)
PSA[2]	0.76	(0.68 - 0.85)	0.77	(0.67 - 0.88)	0.75	(0.61 - 0.93)
% positive cores	0.75	(0.66 - 0.84)	0.76	(0.66 - 0.87)	0.72	(0.58 - 0.89)
mode of detection	0.76	(0.68 - 0.86)	0.77	(0.68 - 0.89)	0.74	(0.59 - 0.92)
Education	0.77	(0.68 - 0.87)	0.79	(0.68 - 0.90)	0.75	(0.60 - 0.93)
Civil Status	0.78	(0.69 - 0.88)	0.79	(0.69 - 0.90)	0.75	(0.60 - 0.93)

The ORs are taken from a multivariate model including all covariates listed

[1]Calculated excluding diabetes
[2]For PSA linear splines with knots at 3, 10 and 20 were used
[3]Cardiovascular disease, hypertension and high cholesterol were defined by filled prescriptions drugs for these conditions in the Prescribed Drug Register

Figure 18: Overall survival for men with type 2 diabetes mellitus according to prostate cancer risk category and prostate cancer treatment in the study Association between Type 2 diabetes, curative treatment and survival in men with intermediate and high risk localised prostate cancer

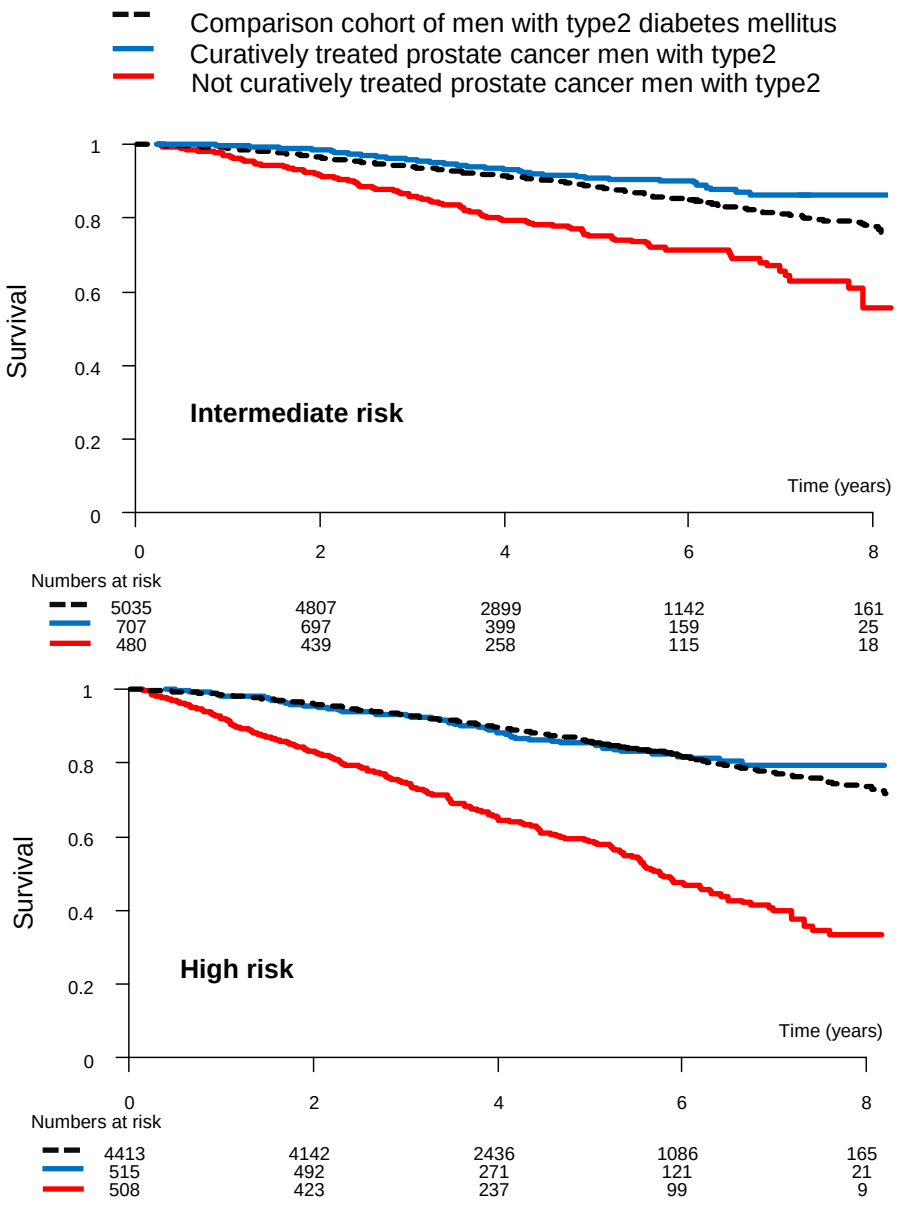
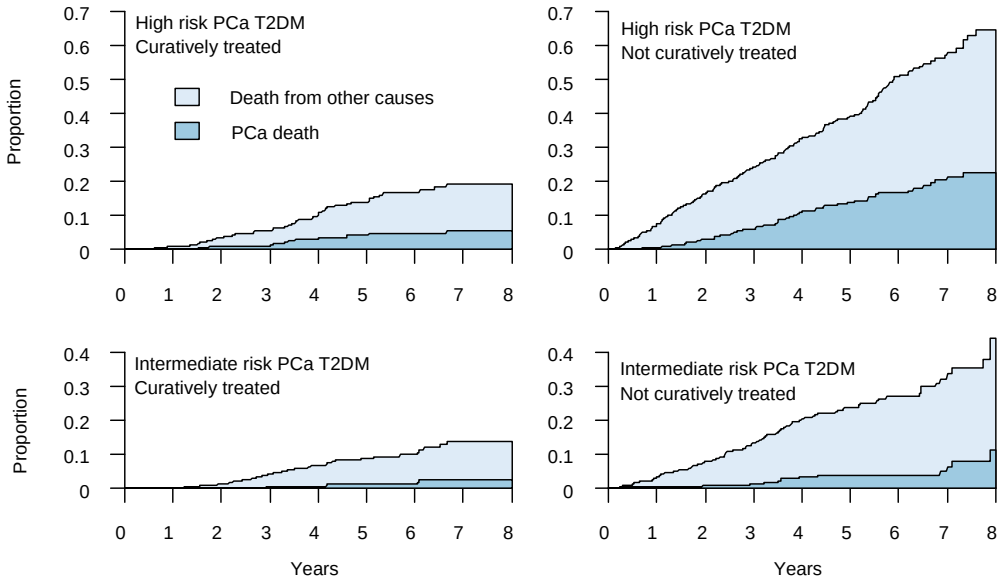


Figure 19: Cumulative incidence of prostate cancer death and death from other causes according to prostate cancer risk category and prostate cancer treatment in study Association between Type 2 diabetes, curative treatment and survival in men with intermediate and high risk localised prostate cancer



Discussion

Men with T2DM were less likely to receive curative treatment for localised PCa, particularly those receiving insulin. While men with T2DM and high risk PCa who did receive curative treatment had substantially higher survival compared to men with T2DM and PCa who were conservatively treated, those selected for curative treatment were found to be the healthiest patients.

Comorbidities affect 10-year mortality more than PCa-mortality in men with conservatively treated localised PCa (165, 167, 171), which has led to the recommendation that men should have a 10 year life expectancy or more in order for a curative treatment to be indicated (168). However, it is difficult to predict an individual's 10 year life expectancy and none of the existing nomograms, which help calculate this, are currently widely used in clinical practice (172).

The impact of comorbidity and age on treatment and survival of men with PCa has been investigated in a Dutch study of over 6,000 men (173). The proportion of men aged 60–69 years who underwent RP decreased significantly from 32% of men without comorbidity to 17% of men with two or more comorbid conditions. This proportion decreased further from 8% to 3% in those aged 70–79 years. A previous study using data from PCBaSe demonstrated that as CCI score increased, men were more likely to receive RT than RP (174). Our study findings are in line with these observations even after taking into account a wide range of potential confounders (age, comorbidities and cancer characteristics).

However, to interpret our findings, it is important to evaluate life expectancy as outlined in the guidelines for PCa treatment (168). The life expectancy of a Swedish man at age 65 is 19 years, with similar figures seen across Europe (12). T2DM may decrease life expectancy by up to 10 years (48). However, men with PCa and T2DM who received curative treatment in our study had a substantially higher OS than men with T2DM and PCa who received conservative treatment. The selection of the healthiest men and allocation to curative treatment among men with T2DM and PCa was indicated by the fact that these men had a better OS than corresponding PCa-free men with T2DM (**Figure 18**). The selection of healthy men for curative treatment is also highlighted by the lower 90-day mortality after RP compared with the background population in a previous Swedish study (175). Williams *et al*. have also demonstrated this selection bias showing a survival advantage in men receiving both RP and RT compared to a PCa free comparison cohort (176). This selection is also seen here in PCa mortality (**Figure19**), which

remained low regardless of PCa treatment for intermediate risk disease. The higher proportion of death from other causes in men not curatively treated confirms that these men have high co-morbidity with ensuing increased risk of death from competing causes. However, in men with conservatively treated high risk PCa, 22% died of PCa within eight years of diagnosis, suggesting that a larger proportion of these men should have received curative treatment. In this study, men with T2DM were more likely to receive primary ADT than those without T2DM (25% vs.15%) (**Table 13**). Given the metabolic and cardiovascular side effects of ADT, this is another reason to ensure that men with PCa and T2DM are not undertreated with respect to curative treatment.

Strengths of this study are its large size, the population-based design and the comparison cohort of PCa-free men with T2DM. Furthermore, it benefits from access to data from a number of nationwide population-based high-quality registers including the Prescribed Drug Register, the Inpatient Register, the Cause of Death Register and the NDR. Limitations include that there was only eight years of follow-up instead of the conventional 10 year survival curves or estimated life expectancies. A further limitation is that by using drug prescriptions as a proxy for T2DM, all cases which were treated by diet alone were not included. However, diet controlled T2DM is unlikely to have influenced PCa treatment decisions. We show that in fact, it is only those treated with insulin who are less likely to receive curative treatment. As discussed above it must be acknowledged that a selection bias of the healthiest men to receive curative treatment among men with T2DM and PCa exists. This was indicated by the fact that these men had a better OS than corresponding PCa-free men with T2DM. There may also be confounding by indication which influenced selection for curative treatment, i.e. those with the most favourable prognosis may have preferentially been chosen for curative treatment. By adjusting for tumour characteristics this has been accounted for as much as possible, however, as with all observational data there may be some residual confounding.

Conclusion

Men with T2DM were less likely to receive curative treatment for localised PCa. Those men with T2DM and high risk prostate cancer who received curative treatment had substantially higher survival, compared to men with T2DM and PCa who were conservatively treated. Some of the survival differences represent a selection bias of the healthiest patients to receive curative treatment. However, in men with conservatively treated high risk PCa, 22% died specifically of PCa, suggesting that a larger proportion of these men should have received curative treatment. Clinicians need to interpret such data carefully and ensure that individual patients with T2DM and PCa are not under nor over treated unnecessarily.

Impact of a prostate cancer diagnosis on existing diabetes treatment

This study has been accepted for an oral presentation at the Annual NCRI Conference in Liverpool, November 2017 (**Appendix 2**). It is also under review for publication with Diabetes Care.

Rationale

With the rapid emergence of several new treatments for PCa in the last six years (32) and survival rates improving, even men with advanced disease may live for many years (177). Hence, the need to understand the complex relationship between PCa and T2DM is increasingly important for clinicians treating both conditions. The systematic review in Chapter III highlighted a gap in the existing literature examining the impact of PCa and its treatments on the control and management of pre-existing T2DM. This study further investigates the impact of a PCa diagnosis on the pharmacological management of T2DM using data from PCBaSe.

Method

Study population and data collection

Using PCBaSe 3.0 this study included all men with a diagnosis of T2DM, without a pre-existing PCa diagnosis, taken either from the NDR or those receiving anti-diabetic medications within the Prescribed Drug Register between 2005 and 2014. The Regional Research Ethics Board at Umeå University approved this study.

The main outcome variable in this study was a change in T2DM treatment (i.e. change from diet-control to metformin or SU or Insulin). Information on filled prescriptions of metformin, SU and insulin were obtained from the Prescribed Drug Register using ATC codes (insulin- ANA, metformin- A10BA/BD, sulphonylurea- A10BB). The initial T2DM treatment was defined using drug prescriptions for anti-diabetic drugs entered in a six month run in following the date of registration of T2DM in the NDR. If the same drug was used in two consecutive 90 day periods it was deemed to be the initial T2DM treatment. Follow-up started after the run-in and if no drug prescriptions had been filled during that period, then diet control was deemed to be the initial treatment. All men who received insulin as initial treatment were excluded from the study, since escalation of insulin doses could not be assessed due to an absence of data on dose.

The main exposure variable in this study was a diagnosis of PCa taken from PCBaSe[trajject]. PCa treatments, divided into no ADT, anti-androgens (AA) and GnRH agonists, were also examined. Exposure to these treatments was taken from the Prescribed Drug Register. If a patient received more than one of these treatments, they contributed exposure time to each category for the duration of that therapy, i.e. a man could have contributed person time to the no ADT group initially and then later to the GnRH agonist or AA exposure group after starting hormonal therapy.

Analysis

Multivariate cox proportional hazards regression was used to calculate hazard ratios and 95% CI for one and two T2DM treatment changes in men who had and had not been diagnosed with PCa. Age was used as a timescale and all models were adjusted for education status and initial T2DM treatment. A further analysis in which the exposure was defined as type of PCa treatment received (as defined above) was then performed. An analysis examining the risk of consecutive treatment changes in patients whose PCa diagnosis came before and after the first treatment change was also performed.

All data management was performed with SAS version 9.3 (SAS Institute, Cary, NC) and all data analysis was conducted with R version 2.13.2 (R Foundation for Statistical Computing, Wien, Austria).

Results

16,778 men with T2DM were included in the study of which 962 were diagnosed with PCa during a median follow up of 2.5 years (**Table 16**). 9692 men (57%) were initially treated with diet control and 6373 (38%) received metformin as their initial T2DM treatment (**Table 16**). All baseline characteristics were similar between those who were and were not diagnosed with PCa. **Table 17** shows the single treatment changes captured and the event numbers for each change for all men. 6,205 treatment changes were seen, the commonest change was from diet control to metformin (3495). 1,191 men had two consecutive treatment changes (**Table 18**).

There was no association between PCa diagnosis and risk of a single treatment change (HR: 0.99; 95%CI: 0.87-1.13) (**Table 19**). Neither was there any association with the type of PCa treatment received (no ADT HR: 0.97; 95%CI: 0.83-1.14, AA HR: 0.80; 95%CI: 0.48-1.36, GnRH agonists HR: 1.12; 95%CI: 0.86-1.47) (**Table 19**).

PCa diagnosis was associated with an increased risk of receiving two consecutive T2DM treatment changes (HR: 1.75; 95%CI: 1.38-2.22) (**Table 20**). This increase was strongest in men on GnRH agonists (HR: 3.08; 95%CI: 2.14-4.40). The corresponding HR for men with PCa not on ADT was 1.40 (95%CI: 1.03-1.92) and for men on AA was 0.91 (95%CI: 0.29-2.82) (**Table 20**). The increased risk was seen only in those who were diagnosed with PCa after a change of T2DM treatment, i.e. who were treated with a drug (HR: 3.59, 95%CI: 2.61-4.93), compared to those who were diagnosed with PCa prior to any change in T2DM treatment (HR: 1.09; 95%CI: 0.78-1.54).

Table 18: Patient characteristics for all patients and divided by those later diagnosed with Prostate Cancer (PCa) and those who were not from PCBaSe included in the study Impact of a prostate cancer diagnosis on existing diabetes treatment

	All Men		No PCa		PCa	
	N=16778		N=15816		N=962	
Age onset of DM (median)		**Q1-Q3**		**Q1-Q3**		**Q1-Q3**
	71.1	(65.5 - 77.2)	71.2	(65.6 - 77.3)	69	(63.1 - 75.5)
Follow Up years (median)		**Q1-Q3**		**Q1-Q3**		**Q1-Q3**
	2.5	(1.1-4.3)	2.5	(1.1-4.3)	3.2	(1.5-5.2)
Initial DM treatment		**%**		**%**		**%**
Diet	9692	57.8	9126	57.7	566	58.8
Metformin	6373	38	6020	38.1	353	36.7
Metformin+SU[1]	79	0.5	75	0.5	4	0.4
SU[1]	634	3.8	595	3.8	39	4.1
HBA1c at DM Onset (%)		**Q1-Q3**		**Q1-Q3**		**Q1-Q3**
	48	43 - 56	48	43 - 56	48	43 - 55
Missing Hba1c (N)		**%**		**%**		**%**
	2310	13.8	2208	14	102	10.6
BMI[2] Median (kg/m^2)		**Q1-Q3**		**Q1-Q3**		**Q1-Q3**
	28.7	26 - 31.6	28.6	26 - 31.6	28.7	26.2 - 31.4
Missing BMI[2] (N)		**%**		**%**		**%**
	4540	27.1	4305	27.2	235	24.4
Education Status		**%**		**%**		**%**
Low	7402	44.1	6998	44.2	404	42
Middle	6336	37.8	5976	37.8	360	37.4
High	2810	16.7	2623	16.6	187	19.4
Missing	230	1.4	219	1.4	11	1.1
Civil Status		**%**		**%**		**%**
Not married	5649	33.7	5317	33.6	332	34.5
Married	11129	66.3	10499	66.4	630	65.5

[1]SU = Sulphonylurea [2]BMI = Body Mass Index

Table 19: Single Treatment changes and event numbers in study Impact of a prostate cancer diagnosis on existing diabetes treatment

One Treatment Change	Event Number
No Change	10,573
Diet -> Metformin	3495
Diet -> SU	389
Metformin -> Insulin	695
Metformin -> SU	770
Metformin + SU -> Insulin	79
SU -> Insulin	129
SU -> Metformin	212
Diet -> Metformin +SU	19
Diet -> Insulin	417

SU = Sulphonylurea

Table 20: Two consecutive treatment changes and event numbers in study Impact of a prostate cancer diagnosis on diabetes treatment

Two Treatment Changes	Event Numbers
No changes	10573
One Change	1320
SU -> Metformin -> Insulin	66
SU -> Metformin + SU -> Insulin	8
Diet -> Metformin -> Insulin	314
Diet -> Metformin -> SU	450
Diet -> SU -> Insulin	60
Diet -> SU -> Metformin	96
Metformin -> SU -> Insulin	197

SU = Sulphonylurea

Table 21: Hazard Ratios and 95% confidence intervals (CI) for a single change of type 2 diabetes mellitus (T2DM) treatment by Prostate Cancer (PCa) diagnosis and PCa treatments in study Impact of a prostate cancer diagnosis on existing diabetes treatment

		Multivariate Analysis[1]	
PCa diagnosis	No PCa	1	REF
	PCa	0.99	0.87-1.13
PCa treatment	No PCa	1	REF
	No ADT[2]	0.97	0.83-1.14
	AA[3]	0.80	0.48-1.36
	GnRH[4]	1.12	0.86-1.47

[1]Multivariate analysis with age as timescale and adjusted for education status and initial diabetes treatment

[2]ADT – Androgen Deprivation Therapy

[3]AA – Anti androgen

[4]GnRH- Gonadotropin-releasing hormone agonist

Table 22: Hazard Ratios and 95% confidence intervals (CI) for two consecutive changes of type 2 diabetes mellitus (T2DM) treatment by Prostate Cancer (PCa) diagnosis and PCa treatments in study Impact of a prostate cancer diagnosis on existing diabetes treatment

	Multivariate Analysis[1]		
PCa diagnosis	No PCa	1.00	(Ref)
	PCa	1.75	1.38-2.22
PCa treatment	No PCa	1.00	(Ref)
	No ADT[2]	1.40	1.03-1.92
	AA[3]	0.91	0.29-2.82
	GNRH[4]	3.08	2.14-4.44
PCa diagnosis in relation to prior change in T2DM treatment	No PCa	1.00	(Ref)
	PCa prior to 1 change	1.09	0.78-1.54
	PCa after 1 change	3.59	2.61-4.93

[1]Multivariate analysis with age as timescale and adjusted for education status and initial diabetes treatment

[2]ADT – Androgen Deprivation Therapy

[3]AA – Anti androgen

[4]GnRH- Gonadotropin-releasing hormone agonist

Discussion

In this population-based cohort study, PCa diagnosis was associated with an increased risk of two consecutive T2DM treatment escalations. The association was strongest in those men treated with GnRH agonists and in men who were receiving pharmacological treatment for their T2DM.

Prior to this study, all studies examining worsening of glycaemic control and T2DM treatments following a PCa diagnosis have focused solely on patients receiving ADT. In a small study of 29 patients with advanced PCa and insulin dependent T2DM receiving ADT, Haidar *et al*. showed a worsening in HBA1c and increasing insulin requirements (178). In a similar US study in 77 patients with T2DM and PCa receiving ADT, 15 (19.5%) had a >10% increase in HBA1c (154). However, there were no control men in either of these small single institution studies. The largest study to date used the Veterans Affairs observational cohort to study 2,237 pairs of propensity matched men with PCa and T2DM who were or were not treated with GnRH agonists (153). They showed an increase in HBA1c at one and two years despite a 20% increased risk of receiving additional T2DM medications in those receiving GnRH agonists. Most recently, a case-control study showed no impact of PCa diagnosis on mean HbA1c or glucose (179). However, over 70% of patients in this study underwent a radical prostatectomy and therefore did not receive ADT.

These studies are in line with the findings of the current study that a diagnosis of PCa worsens glycaemic control in men with pre-existing T2DM when looking at the proxy of escalating pharmacological treatment. Worsening of glycaemic control was strongest in men on GnRH agonists compared to other forms of ADT such as AA. This mirrors what has previously been seen with the increased risk of T2DM in non-diabetics treated with ADT (139), which is presented below. However, we also show an increased risk of two consecutive treatment escalations in those who are not receiving any form of ADT. Current literature has focused only on those receiving ADT, so this is a new finding. This may suggest that there is a true disease effect of PCa on glycaemic control, not just as a result of treatments received.

This study showed no increase in risk of a single treatment change in those diagnosed with PCa. The risk was highest in those who already had one escalation of treatment prior to the diagnosis of PCa. As nearly 60% of the study population was initially treated with dietary modification, this suggests those who are already receiving a pharmacological treatment for T2DM are at highest risk of

further escalations following a PCa diagnosis. This is in concordance with previous studies. Keating *et al.* looked specifically at initiation or addition of insulin therapy and found a higher rate in men on ADT vs men not on ADT (94.5 men per 1,000 person-years vs. 81.2), as a marker of intensification of anti-diabetes management (153).

Biologically, this is not unexpected, as it is known that ADT, particularly GnRH agonists, leads to an increase in body fat and a decrease in insulin sensitivity. These physiological effects have been shown to occur early after treatment initiation (180) and although it has not been directly studied it can be hypothesised that similar physiological changes would occur in patients with pre-existing diabetes leading to a worsening of glycaemic control and the need for escalating pharmacological management.

Strengths of this study are the large population design of PCBaSe^{traject} and the large number of men with T2DM included. The design of the study allows for inclusion of a large number of men who subsequently developed PCa. The linkage to both the NDR and Prescribed Drug Register allowed detailed data on the initial and subsequent T2DM treatments to be accessed. Unlike previous studies, here detailed data was available on the type of PCa treatment being received and enabling examination of GnRH agonists individually, not only in combination with other forms of ADT. Weaknesses include the lack of repeated measures of HBA1c, so although it was possible to present median HBA1c at T2DM diagnosis there was insufficient data available to examine changes following a PCa diagnosis. However, using change in T2DM treatments as a proxy of worsening glycaemic control is a clinically relevant outcome. Patients who had insulin dependent T2DM at diagnosis were excluded from the study, as data to capture change in insulin doses was not available. However, it is unusual for a person with newly diagnosed T2DM to require insulin as first line treatment. By using a six month run in window, with consecutive 90 day periods, to determine initial T2DM treatment, it was still possible to include any patients who needed a one-off period of insulin to rapidly achieve glycaemic control at presentation before moving on to different forms of maintenance treatment. Hence, the numbers lost because of this exclusion were small.

Conclusion

This study has shown that men with T2DM who are diagnosed with PCa, particularly those treated with GnRH agonists, are more likely to have two

consecutive treatment escalations in T2DM treatment. This suggests a need for closer monitoring of men with both PCa and T2DM, as co-existence of PCa and its subsequent treatments could potentially worsen T2DM control.

Association between duration and type of ADT and risk of diabetes in men with prostate cancer

This study was presented as a poster presentation at the Annual NCRI Conference in Liverpool 2015 and was subsequently published in the International Journal of Cancer in Dec 2016 (139). It was also shortlisted for the Sylvia Lawler Prize and presented at the Royal College of Physicians in June 2016 (Appendix 3).

Rationale

As discussed in Chapters II and III, ADT is the recommended first line treatment in all men with advanced PCa and is also used in conjunction with radiotherapy in locally advanced disease as both neoadjuvant and adjuvant therapy. When men progress to castration resistance, it is recommended that treatment with ADT continues, alongside the addition of further therapies (32). Given the prolonged disease trajectory of PCa, men can remain on ADT for many years (181), making any long-term effects associated with treatment significant. As presented in Chapter III, several North American cohorts have demonstrated an increased risk of diabetes (88, 132-134). In 2010 this led the FDA to add a risk label on GnRH agonists for increased risk of T2DM and certain cardiovascular diseases (heart attack, sudden cardiac death and stroke) (135). Using data from PCBaSe, this study investigates the risk of T2DM taking into account the impact of different types and durations of ADT (GnRH agonists, AA, and orchiectomy) on risk of T2DM.

Method

Study population and data collection

This study used PCBaSe 3.0, as described in detail above. Information on filled prescriptions of AA, GnRH agonists, metformin, SU and insulin was obtained from the Prescribed Drug Register using ATC codes (insulin- ANA, metformin- A10BA/BD sulphonylurea- A10BB GnRH –L02AE AA- L02BB). The Research Ethics Board at Umeå University approved this study.

Both men who received primary and secondary ADT, i.e. as a second line treatment strategy initiated after primary treatment at the time of disease progression were included in the study. Primary treatment was recorded in NPCR as well as the Prescribed Drug Register, whereas secondary ADT was retrieved from the Prescribed Drug Register only (156). Co-morbidities were measured by the CCI, which is also described in detail above.

Analysis

An analysis whereby PCa men on ADT and PCa-free men were followed to identify occurrence of T2DM was conducted. The main outcome T2DM was defined as two filled prescriptions for insulin, metformin or sulphonylurea with a maximum time between the two prescriptions of 180 days. The date of the first filled prescription was used as the date of the event. HRs for T2DM were calculated for men with PCa versus the comparison cohort with left truncation using a Cox proportional hazards model with age as a timescale accounting for CCI, PCa risk category and education status. Left truncation was applied because the Prescribed Drug Register started on July 1st 2005. This allowed for a run-in period of six months and men with a filled prescription for anti-diabetic drugs during this period were excluded from the analysis. Hence, all men with prevalent T2DM on an anti-diabetic drug were excluded. Follow up started on 1st January 2006 and ended at date of death, date of emigration, date of T2DM prescription, or 31 December 2013, whichever came first. Men who received AA or GnRH according to NPCR and had a date of diagnosis prior to 1st January 2006 and were found to still be receiving them according to the Prescribed Drug Register during the "run in period" were considered to have been ''exposed'' since the date of diagnosis (120). All other exposure to AA or GNRH was defined as time from first filled prescription. In case of cross over, patients were allowed to change groups and were from then onwards considered to be exposed to the treatment in their new group. Thereby, these persons contributed person/years in each treatment category.

The association between duration of ADT and risk of T2DM was assessed using multivariate Cox proportional hazards models with left truncation in which exposure time was divided into the following intervals: 0-6 months, 6-12 months, 12-18 months, 18-24 months, 24-30 months, 30-36 months, 36-48 months, 48-60 months, 60-72 months, 72-84 months, 84-120 months, >120 months. Incidence rates per 1,000/person years for the different exposure groups were then calculated.

Finally, a sensitivity analysis was conducted in which incidence rates of T2DM were compared between men with PCa two years prior to initiation of ADT and men two years post initiation of ADT. This analysis included men free of T2DM who received their first ADT after 1st of August 2008 to ensure that sufficient data was available from the Prescribed Drug Register which only start on 1st July 2005.Those men in the sensitivity analysis who developed T2DM in the period 0-2 years prior to ADT were not included in the overall analysis.

All data management was performed with SAS version 9.3 (SAS Institute, Cary, NC) and all data analysis was conducted with R version 2.13.2 (R Foundation for Statistical Computing, Wien, Austria).

Results

167,205 PCa-free men and 34,031 men with PCa out of whom 21,874 (64%) received GnRH agonists, 9,143 (27%) AA and 3,014 (9%) underwent orchiectomy were included in the study (**Table 21**). Results for men who had undergone surgical or medical castration were analysed together in the GnRH/Orch group.

There was a five-fold higher occurrence of metastatic disease at date of diagnosis among men in the GnRH compared to men on AA (32% vs 6%). Conversely, five times as many men on AA had undergone primary curative treatment and subsequently received ADT, compared to men on GnRH (31% vs. 6%)(**Table 21**).

Table 22 shows the number of events and HRs for men receiving a new prescription for insulin, SU or metformin on AA or GnRH/Orch over time compared to a PCa free cohort. Those in the GnRH/Orch group had an increased risk, up until 2.5-3 years of exposure, HR 1-1.5 years of ADT 1.61 (95%CI: 1.36- 1.91), 2-2.5 years of ADT 1.68 (95%CI:1.4-2.02), 2.5-3 years of ADT 1.42 (95%CI: 1.16-1.76) which then reduced, 3-4 years of ADT 1.17 (95% CI: 0.98- 1.40) and 7-10 years ADT 0.96 (95% CI: 0.77-1.19). In contrast, those on AA had no increased risk of T2DM during any time period compared to PCa-free men, HR during 0-2 years of ADT 0.73 (95% CI: 0.61-0.87), 2-4 years: 0.71 (95% CI: 0.56-0.91) and >4 years 0.80 (95% CI: 0.61-1.05).

In the subgroup of men treated with insulin only (**Table 22**), there was a persistent increase in risk observed during all time periods for men in the GnRH/Orch group, peaking at 2.5- 3 years with a HR of 2.32 (95%CI: 1.67-3.21). In contrast, those on AA had no increased risk of T2DM during any time period compared to PCa-free men. **Table 22** reports the corresponding results for those receiving either metformin or sulphonylurea. Those in the GnRH/Orch group had a significantly elevated risk until 2-2.5 years of exposure (HR: 1.65, 95% CI: 1.35-2.02) before a reduction in later time periods which became non-statistically significant. Similarly to insulin, no increased risk of T2DM was seen in those on AA at any time period. The time-dependent results of **Table 22** are also illustrated in **Figure 20**.

The incidence of T2DM for those without ADT was 10/1,000 person-years, for men on GnRH agonists/orchiectomy 13/1,000 person-years and 8/1,000 person-years for men on AA (**Table 23**).

The results of the sensitivity analysis comparing the incidence of T2DM in men with PCa two years prior and after initiation of ADT are presented in **Table 24**. A similar increase in risk for T2DM was observed. In men treated with AA the incidence of T2DM (receiving insulin) was 1.5 vs 1.7/1,000 person-years two years before and after ADT. In those treated with GnRH/Orch, the incidence of T2DM (receiving insulin) was 2.2 vs 5.0/1,000 person-years, respectively, and for T2DM (receiving metformin/SU) 11.1 vs. 11.3/1,000 person-years.

Table 23: Baseline characteristics of men with prostate cancer (PCa) on androgen deprivation therapy (ADT) and the matched comparison cohort of PCa-free men in Prostate Cancer Data Base included in the study Association between duration and type of ADT and risk

	PCa Free Cohort		All men with PCa		AA		GnRH		Orchiectomy	
n (%)	167,205		34,031		9,143		21,874		3,014	
Mean Follow up time (SD)										
	4.2	(2.5)	3.5	(2.4)	3.6	(2.3)	3.5	(2.4)	3.1	(2.4)
Age										
Mean age at diagnosis (SD)	74.8	(8.5)	74.4	(8.4)	71.2	(8.0)	75.2	(8.3)	78.4	(7.3)
<65	23183	(13.9)	4908	(14.4)	2119	(23.2)	2623	(12.0)	166	(5.5)
65-74	55348	(33.1)	11806	(34.7)	3893	(42.6)	7247	(33.1)	666	(22.1)
75-84	70809	(42.3)	14136	(41.5)	2829	(30.9)	9655	(44.1)	1652	(54.8)
85+	17865	(10.7)	3181	(9.3)	302	(3.3)	2349	(10.7)	530	(17.6)
Age at start of ADT										
<65	-	-	3592	(10.6)	1189	(13.0)	2254	(10.3)	149	(4.9)
65-74	-	-	10849	(31.9)	3641	(39.8)	6596	(30.2)	612	(20.3)
75-84	-	-	15493	(45.5)	3766	(41.2)	10059	(46.0)	1668	(55.3)
85+	-	-	4097	(12.0)	547	(6.0)	2965	(13.6)	585	(19.4)
Entry into PCBaSe cohort/ Year of PCa diagnosis										
1997-2001	17889	(10.7)	5389	(15.8)	1145	(12.5)	3687	(16.9)	557	(18.5)
2002-2005	49375	(29.5)	11281	(33.1)	2738	(29.9)	7446	(34.0)	1097	(36.4)
2006-2009	64085	(38.3)	11567	(34.0)	3438	(37.6)	7161	(32.7)	968	(32.1)
2010-2012	35856	(21.4)	5794	(17.0)	1822	(19.9)	3580	(16.4)	392	(13.0)
CCI										
0	110713	(66.2)	22328	(65.6)	6271	(68.6)	14143	(64.7)	1914	(63.5)
1	29651	(17.7)	6247	(18.4)	1587	(17.4)	4048	(18.5)	612	(20.3)
2	15948	(9.5)	3309	(9.7)	793	(8.7)	2215	(10.1)	301	(10.0)
3+	10893	(6.5)	2147	(6.3)	492	(5.4)	1468	(6.7)	187	(6.2)
Education Status										
Low	78732	(47.1)	16239	(47.7)	3559	(38.9)	10898	(49.8)	1782	(59.1)
Middle	56051	(33.5)	11579	(34.0)	3422	(37.4)	7252	(33.2)	905	(30.0)
High	29171	(17.4)	5771	(17.0)	2091	(22.9)	3403	(15.6)	277	(9.2)
Missing	3251	(1.9)	442	(1.3)	71	(0.8)	321	(1.5)	50	(1.7)

PCa risk category										
No PCa	167205	(100.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
1. Low risk	-	-	2334	(6.9)	1180	(12.9)	1068	(4.9)	86	(2.9)
2. Intermediate risk	-	-	6021	(17.7)	2819	(30.8)	2929	(13.4)	273	(9.1)
3. High risk	-	-	11775	(34.6)	3469	(37.9)	7410	(33.9)	896	(29.7)
4. Regionally metastatic	-	-	4745	(13.9)	962	(10.5)	3354	(15.3)	429	(14.2)
5. Distant metastases	-	-	8850	(26.0)	591	(6.5)	6956	(31.8)	1303	(43.2)
6. Missing data	-	-	306	(0.9)	122	(1.3)	157	(0.7)	27	(0.9)
Primary Treatment										
No PCa	167205	(100.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
ADT	-	-	24815	(72.9)	4113	(45.0)	17972	(82.2)	2730	(90.6)
Curative treatment	-	-	4352	(12.8)	2887	(31.6)	1402	(6.4)	63	(2.1)
Deferred treatment	-	-	4864	(14.3)	2143	(23.4)	2500	(11.4)	221	(7.3)

	Insulin/sulphonylurea/metformin					Insulin					Sulphonylurea /metformin				
ADT years of exposure	No Events	Crude HR	95% CI	Adjusted HR*	95% CI	No Events	Crude HR	95% CI	Adjusted HR*	95% CI	No Events	Crude HR	95%CI	Adjusted HR*	95%CI
No ADT	7932	1	Ref.	1	Ref.	1688	1	Ref.	1	Ref.	6320	1	Ref.	1	Ref.
AA 0-2	126	0.73	(0.61 - 0.88)	0.73	(0.61 - 0.87)	27	0.78	(0.53 - 1.14)	0.76	(0.52 - 1.11)	100	0.67	(0.55 - 0.82)	0.68	(0.56 - 0.83)
AA 2-4	71	0.7	(0.54 - 0.89)	0.71	(0.56 - 0.91)	16	0.82	(0.50 - 1.34)	0.83	(0.51 - 1.36)	55	0.69	(0.53 - 0.90)	0.71	(0.54 - 0.92)
AA >4	61	0.76	(0.58 - 0.99)	0.8	(0.61 - 1.05)	9	0.54	(0.28 - 1.05)	0.59	(0.30 - 1.13)	52	0.84	(0.64 - 1.10)	0.88	(0.67 - 1.16)
GnRH 0 -0.5	157	1.44	(1.23 - 1.70)	1.41	(1.20 - 1.67)	36	1.52	(1.09 - 2.12)	1.31	(0.93 - 1.85)	124	1.35	(1.13 - 1.61)	1.38	(1.15 - 1.66)
GnRH 0.5 -1	162	1.54	(1.31 - 1.80)	1.51	(1.28 - 1.79)	41	1.82	(1.33 - 2.47)	1.59	(1.15 - 2.19)	126	1.45	(1.21 - 1.73)	1.49	(1.24 - 1.80)
GnRH 1-1.5	156	1.62	(1.38 - 1.91)	1.61	(1.36 - 1.91)	40	1.91	(1.40 - 2.62)	1.71	(1.24 - 2.37)	120	1.52	(1.27 - 1.82)	1.58	(1.31 - 1.90)
GNRH 1.5-2	132	1.47	(1.23 - 1.76)	1.48	(1.23 - 1.78)	35	1.84	(1.32 - 2.57)	1.67	(1.18 - 2.36)	100	1.4	(1.15 - 1.71)	1.46	(1.19 - 1.79)
GnRH 2-2.5	132	1.67	(1.40 - 2.00)	1.68	(1.40 - 2.02)	34	1.96	(1.40 - 2.76)	1.81	(1.27 - 2.56)	102	1.59	(1.30 - 1.93)	1.65	(1.35 - 2.02)
GnRH 2.5-3	104	1.41	(1.15 - 1.73)	1.42	(1.16 - 1.76)	39	2.49	(1.81 - 3.42)	2.32	(1.67 - 3.21)	67	1.17	(0.92 - 1.49)	1.23	(0.96 - 1.57)
GnRH 3-4	143	1.15	(0.97 - 1.37)	1.17	(0.98 - 1.40)	45	1.66	(1.23 - 2.23)	1.58	(1.16 - 2.14)	100	1.03	(0.85 - 1.26)	1.09	(0.89 - 1.33)
GnRH 4-5	127	1.14	(0.94 - 1.39)	1.19	(0.97 - 1.45)	50	2.27	(1.71 - 3.01)	2.22	(1.65 - 2.97)	78	1.02	(0.82 - 1.28)	1.09	(0.86 - 1.36)
GnRH 5-6	91	1.06	(0.84 - 1.33)	1.11	(0.88 - 1.40)	36	2	(1.44 - 2.79)	2.01	(1.43 - 2.82)	56	0.93	(0.71 - 1.20)	1	(0.76 - 1.30)
GnRH 6-7	67	0.95	(0.72 - 1.24)	1.01	(0.77 - 1.33)	27	1.88	(1.28 - 2.74)	1.91	(1.30 - 2.82)	42	0.88	(0.65 - 1.20)	0.96	(0.71 - 1.31)
GnRH 7-10	101	0.87	(0.71 - 1.08)	0.96	(0.77 - 1.19)	32	1.2	(0.85 - 1.70)	1.28	(0.89 - 1.83)	71	0.85	(0.67 - 1.07)	0.95	(0.74 - 1.20)
GnRH >10	30	0.6	(0.40 - 0.92)	0.69	(0.45 - 1.05)	16	1.51	(0.92 - 2.48)	1.72	(1.04 - 2.84)	15	0.5	(0.30 - 0.83)	0.58	(0.35 - 0.96)

*Adjusted for CCI, PCa Stage, and Education level.

Table 24: Hazard ratios for Insulin, sulphonylurea or metformin in men on ADT compared to a comparison cohort of PCa-free men in the study Association between duration and type of ADT and risk of diabetes in men with prostate cancer

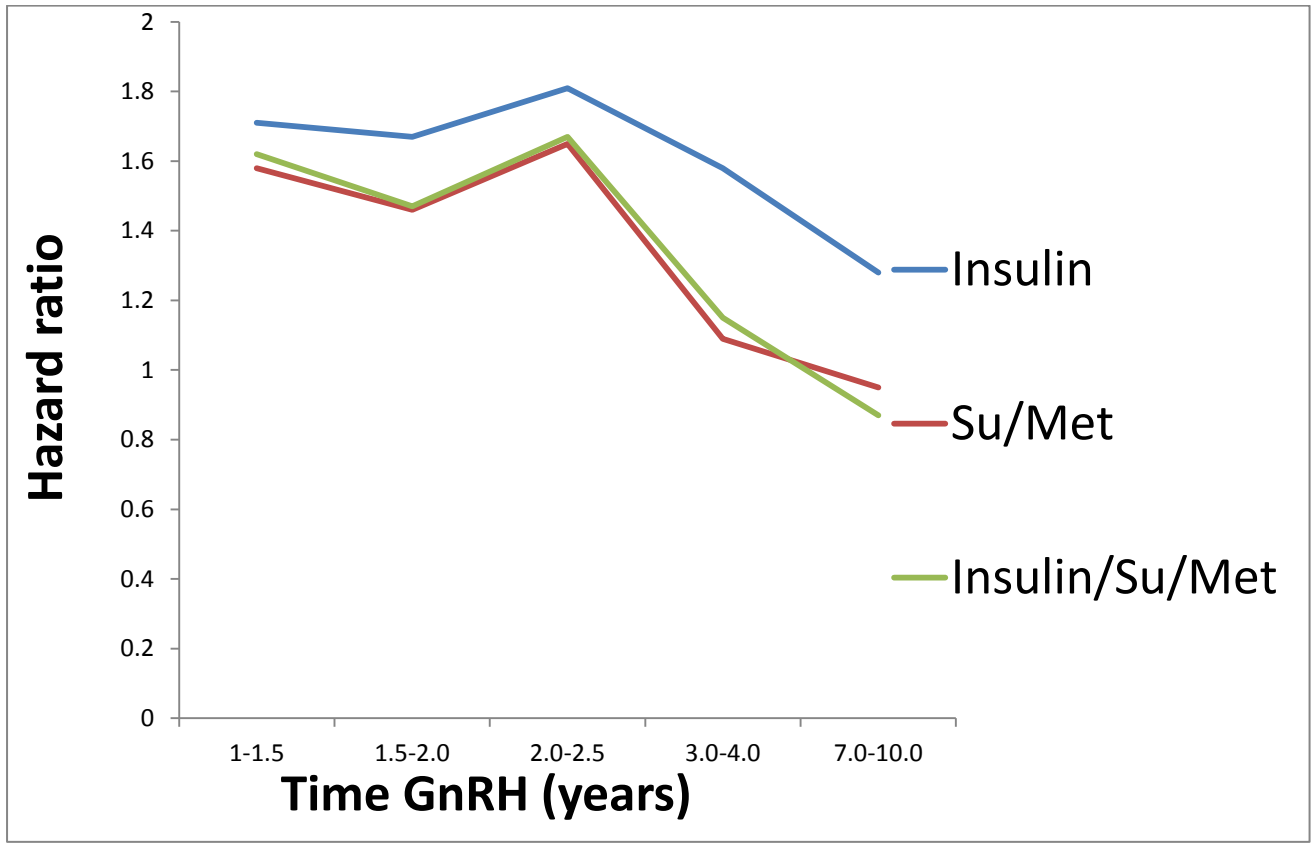
Table 25: Incidence of T2DM per 1,000 person-years in PCa-free men and men with PCa on anti-androgens (AA) or GnRH agonists/orchiectomy (GnRH/Orch group) according to anti-diabetic drug prescriptions in the study Association between duration and type of ADT and risk of diabetes in men with prostate cancer

		Insulin /Sulphonylurea /Metformin		Insulin		Metformin /Sulphonylurea
	No of events	Incidence rate	No of events	Incidence rate	No of events	Incidence rate
No ADT	7274	10.45	1030	1.47	6244	8.97
AA	239	8.07	33	1.11	206	6.96
GNRH/Orch	1258	12.98	287	2.96	971	10.01
Prior AA	81	13.64	11	1.85	70	11.79
No Prior AA	1177	12.93	276	3.03	901	9.90

Table 26: Event number and incidence per 1,000/person years of T2DM treated with Metformin/Sulphonylurea or Insulin in men with PCa two years before and after ADT initiation in the study Association between duration and type of ADT and risk of diabetes in men with prostate cancer

	Metformin/Sulphonylurea				Insulin			
	2 years prior to ADT initiation		2 years after ADT initiation		2 years prior to ADT initiation		2 years after ADT initiation	
Type of ADT at initiation	No DM events	Incidence of DM	No DM events	Incidence of DM	No DM events	Incidence of DM	No DM events	Incidence of DM
All	394	10.4	301	10.1	73	1.9	113	3.8
AA	128	9.1	91	8.1	21	1.5	19	1.7
AA initial treatment	50	9.2	44	9.5	10	1.8	10	2.2
AA deferred treatment	78	9.0	47	7.1	11	1.3	9	1.4
GNRH	266	11.1	210	11.3	52	2.2	94	5.0
GNRH initial treatment	195	10.9	159	11.3	41	2.3	70	5.0
GNRH deferred treatment	71	11.7	51	11.2	11	1.8	24	5.2

Figure 20: Graphical representation of risk of T2DM by time on GnRH agonists, T2DM was defined by anti-diabetic drug prescriptions (a) Insulin, (b) Sulphonylurea or Metformin, (c) Insulin, Sulphonylurea or Metformin in the study Association between duration and type of ADT and risk of diabetes in men with prostate cancer



Discussion

In accordance with previous studies, this large nation-wide population-based cohort study showed that men on ADT had an increased risk of T2DM as defined by filled prescriptions for an anti-diabetic drug. In addition, the highest risk of T2DM was reached at three years after the start of GnRH/Orch. In contrast, men on monotherapy anti-androgens had no such increase.

In the first study on risk of T2DM for men on GnRH agonists, Keating *et al*. showed an increased risk in men aged >66 with loco-regional PCa (HR for GnRH agonists versus no ADT: 1.44, 95% CI: 1.34-1.55) (88). However, this study had a relatively short duration of exposure, i.e. 1-4, 5-12, 13-24, >25 months. The same authors obtained similar results in a further study including men of all ages with loco-regional PCa (134). They analysed combined androgen blockade and AA separately and did not show an increased risk of T2DM. The effect of duration of treatment on risk of T2DM was not examined. A similar study was conducted by Alibhai *et al.* in a Canadian cohort of men aged ≥66 years who received at least 6 months of ADT (132). They also reported an increased risk of T2DM (HR: 1.16, 95% CI: 1.11-1.21), but did not examine GnRH and AA separately and combined all forms of ADT as a single exposure. There was a trend toward increased risk of T2DM with longer exposure to ADT (HR for ADT vs. no ADT: 1.09, 95%CI: 0.9-1.08 >24 months of exposure compared with HR: 0.99, 95%CI: 0.90-1.08 at 6-24 months).

The longest duration of follow up in these studies was 25 months (88). No studies had looked at different types of ADT and the effect of duration combined. AA use in North America is substantially lower than in Europe, so there are little data from these cohorts on AA. In this study the risk of T2DM with up to ten years of exposure was studied, which is to our knowledge the longest exposure studied to date. The highest risk associated with GnRH agonists occurred relatively early and started to decline after three years of treatment. For AA no increased risk was observed.

The observed temporal changes in risk fit with the physiological and metabolic changes previously described for GnRH agonist treatment (180). These changes included increased fat mass, reduced lean body mass and increased insulin levels, which all have been demonstrated to occur within three months of commencing ADT (180, 182, 183). Lee *et al*. measured lean body mass and fat mass in 65 men with PCa on GnRH agonists over a 12 month period. Those with longer prior exposure to treatment with GnRH agonists had less fat accumulation and less loss

of lean body mass over the 12 month period (182). Similarly, GnRH agonists decrease sensitivity to insulin within three months of ADT start (184). Thus, the adverse metabolic effects of GnRH agonists occur within months of initiation; the consequences of these changes (i.e. developing T2DM) do not peak until several years later. The risk then tails off towards null over time. This suggests that those men susceptible to the metabolic effects of GNRH agonists develop T2DM in the first few years of treatment.

Strengths of this study are its large size, population-based design of PCBaSe, and long duration of exposure to ADT. The use of an age-matched PCa-free comparison cohort allowed us to handle PCa heterogeneity. If men with PCa receiving radical therapy or men on active surveillance/watchful waiting had been used as the comparison group this would have introduced selection bias as these men have a different general health status than men with PCa on ADT. However, this approach does not allow us to tease out the disease effect. The sensitivity analysis comparing incidence rates of T2DM in men with PCa two years prior and after initiation of ADT aimed to assess this. The results remained consistent to what was seen when using the PCa free comparison cohort, with a higher incidence of T2DM in those receiving insulin observed after two years of GnRH treatment (2.2 vs 5.0 /1,000 person years) and not in those treated with AA.

One limitation of this study is that by using new drug prescriptions as a proxy for T2DM, T2DM cases treated by diet alone were not included; however, this would be similar for men with and without PCa. It would be interesting in future studies to be able to include this group of men. By only including two of the potential OHAs used for T2DM (metformin and SU) those with T2DM who were on alternative drugs were also not included. However, these only accounted for 1.32% of events in this study. Another limitation is the lack of information about lifestyle factors including weight or family history of T2DM. However, all results were adjusted for CCI, which accounts for other comorbidities associated with lifestyle risk factors (185), as well as education status – which has also been shown to be a good indicator of baseline health status (185). Despite adjusting for several covariates, residual confounding may still be present. However, adjustment for CCI and education status reduces this possibility substantially. A further limitation is that the different risks observed between GnRH agonists and AA could potentially be explained by selection bias, rather than a real difference in the two treatments. Men treated with GnRH agonists are not only more likely to have locally advanced or distantly metastatic disease, they are also more likely to have more comorbidities than those treated with AA.

This reflects standard clinical practice whereby GnRH agonists are used as a primary treatment for advanced disease. Hence, men on GnRH agonists may be at higher risk of T2DM than those on AA; this however, does not diminish the clinical importance of identifying those at highest risk of T2DM during ADT.

Conclusion

The duration of GnRH agonists had a significant impact on risk of T2DM in men with PCa, with the peak risk observed after three years of treatment. This suggests that even men receiving adjuvant ADT, for a short time period, may be at increased risk of T2DM.

Summary of findings in PCBaSe

In this chapter I have used data from PCBaSe to further explore the complex and multidirectional relationship between T2DM and PCa.

Firstly, I have shown that men with T2DM are less likely to receive curative treatment for intermediate or high risk PCa than those without T2DM. Also, in those men with high risk PCa who did not receive curative treatment, a substantial amount died specifically of PCa, suggesting that a larger proportion of these men should potentially have received curative treatment. Hence, this study showed that the concurrent diagnosis of both conditions can impact upon the type of treatment received for PCa.

Secondly, I have found that having both conditions impacts upon the treatment received for T2DM. Men with T2DM diagnosed with PCa are at higher risk of two or more consecutive treatment changes than those not diagnosed with PCa, suggesting a worsening of glycaemic control following a PCa diagnosis.

Finally, the interplay between T2DM and PCa is further complicated by the fact that ADT, used as a treatment of PCa, increases the risk of developing T2DM in men previously free of T2DM. Furthermore, this risk was dependent on both the type and duration of ADT used, with GnRH agonists leading to an increased risk of T2DM which was highest in the first three years of treatment.

Taken together, these studies highlight the need for clinicians treating men with both PCa and T2DM to be aware of the impact that one has on the other and that a

multi-disciplinary approach to their care between endocrinologists, urologists and oncologists is essential to achieve optimal care for both conditions.

Chapter V: Effect of baseline metabolic aberrations in men with advanced prostate cancer treated with ADT on disease progression, prostate cancer-specific and all cause death

This study was presented as a poster presentation at European Society of Medical Oncology (ESMO) Annual conference in 2016 in Copenhagen and was awarded the prize for best poster in the genitourinary, prostate session (Appendix 4). The manuscript of the study is currently under review with the International Journal of Cancer.

Rationale

Some studies have suggested that MetS, or some of its features, are associated with high-grade PCa (186, 187) . As discussed in Chapter III and IV, ADT has been shown to induce a metabolic–like syndrome (6). It has also been suggested that the presence of MetS either at diagnosis or its development after initiation of ADT may identify those men who are at risk of more rapid progression through first-line ADT (86, 87, 188) .

However, this hypothesis has never been investigated in a large cohort of patients. This study examines the effect of baseline metabolic aberrations (T2DM, hypertension, dyslipidaemia and obesity) on outcomes of disease progression, PCa-specific and all cause death in a cohort of men with locally advanced/metastatic PCa starting ADT.

Methods

Study design and population

The study was conducted using a retrospective review of prospectively-collected data of men enrolled in the MRC STAMPEDE trial who were allocated to the control arm, A. STAMPEDE is a MRC-sponsored, National Institute for Health Research (NIHR) Cancer Research Network (CRN)-supported randomised controlled trial for patients with locally advanced or metastatic PCa in the UK and Switzerland (189, 190). The original randomised controlled trial platform opened to accrual in October 2005 with six arms (**Figure 21**). It remains open to recruitment and, to date, has recruited >8000 patients across nine randomised comparisons. It is designed to examine the benefits of treatment additions to standard care ADT and EBRT as relevant. EBRT was mandated for N0 M0 patients from November 2011. At the time of the data freeze on 25th September 2015, the control arm cohort analysed here included 2,622 patients starting long-term ADT (with or without EBRT).

Definition of metabolic aberrations

Data collected within STAMPEDE were assessed to define baseline metabolic aberrations at enrolment into the study. Due to the nature of this analysis using trial data, where calculating metabolic profile was not the main focus, the full set of metabolic baseline data which would fulfil all of the joint statement of major international association's definition of MetS was not available (74). Therefore, here, the data were assessed for the presence or absence of the following metabolic aberrations at baseline:

1. Hypertension (systolic blood pressure ≥140mmHg and/or diastolic blood pressure ≥90mmHg or confirmed history of hypertension)
2. Obesity (BMI >30kg/m2)
3. Dyslipidaemia (HDL <1.9mmol/l)
4. Impaired Glycaemia (confirmed history of T2DM)

These criteria were as close to the joint statement of major international association's definition of MetS as possible from the available data. These metabolic aberrations were then analysed individually and together (as a composite metabolic risk score identifying how many components were present). Those with a composite score of three or more are below referred to as having composite metabolic aberrations (CMA).

Analysis

Cox proportional hazards models were used to estimate hazard ratios and 95% confidence intervals comparing patients with and without baseline CMA, and individual metabolic aberrations, for outcomes of PCa progression and death. PSA, local and metastatic progression were defined as per STAMPEDE trial protocol (189).

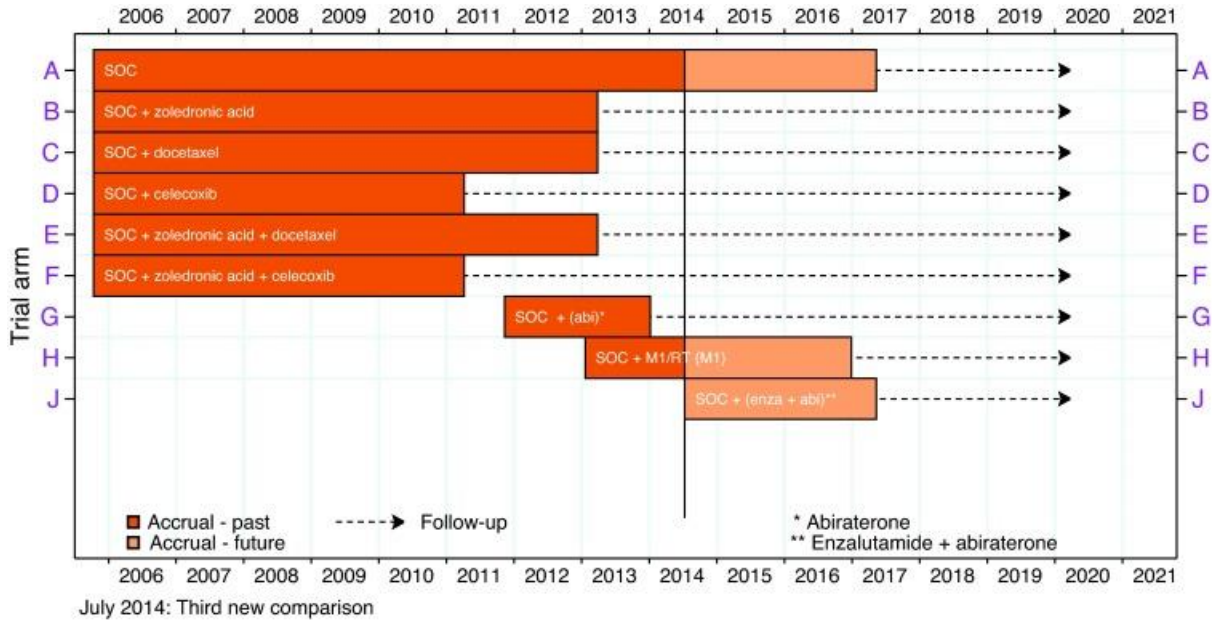
To define PSA progression, the extent of the primary response has to be taken into account. Three groups of patients are defined in the trial: A. If the PSA nadir is more than 50% of the last pre-treatment PSA and the PSA nadir is more than 4ng/ml, the patient should be defined as a treatment failure (at time zero). B. For patients whose PSA nadir is less than or equal to 50% of the last pre-treatment PSA, but remains above 4ng/ml, PSA relapse will be deemed to have occurred when PSA is confirmed as increasing by 50% above the nadir level. C. For patients whose PSA falls below or to 4ng/ml, PSA relapse will be defined by either 50% increase from their nadir or the PSA increasing above 4, whichever is the greater.

For example, a nadir PSA of 3.6 would require a PSA of 5.4 to define relapse, while PSA nadir of 2.5 will be considered to have relapsed at a PSA of 4. The trial protocol states that if the PSA value reaches the progression value, a confirmatory PSA test should be performed between one week and 3 months later. Biochemical failure is confirmed if the second value is around the same level or higher. In patients with measurable baseline disease as per RECIST criteria (191), local and metastatic progression are defined as at least a 20% increase in the sum of target lesions or the appearance of one or more new lesions. Progression (local or metastatic) for patients with non-measurable disease at randomisation is defined as increasing clinical or radiological evidence of disease since study entry.

These outcomes were combined into an overall PCa progression outcome, but were also studied separately. All cause death and PCa-specific death (PCSD) were also investigated. It is important to note that the failure free survival (FFS) end point as used in the STAMPEDE trial previously (189) was not used in this analysis, to allow for consistency with the few pre-existing studies in this area (86, 87, 188).

Univariate and multivariate analyses were performed. The multivariate analysis was adjusted for age, Gleason sum score, PSA pre-ADT, type of long-term ADT and TNM stage. Median follow-up was determined through the standard approach of reverse-censoring on death, in which survival is treated as the event and death as censoring. Competing risk analysis was not performed for the PCSD data as in this cohort of men with advanced disease the importance of other competing risks of death would be less important than when studying men with earlier stages of PCa (192); nor were competing risks used in assessing each type of progression. A stratified analysis according to metastatic status at randomisation was also performed.

Figure 21: Trial Schema for the STAMPEDE trial



Results

A total of 2,622 patients treated with ADT (+/-EBRT) who were randomised to the control arm of STAMPEDE between October 2005 and September 2015 were included in this analysis. The data were frozen on 25th September 2015. Median follow up time in this cohort was 21 months. The patient characteristics are summarised in **Table 25**. Median age at randomisation was 66 years. 2,663 (98%) patients received GnRH agonist treatment. In this population, 1,844 (87%) had dyslipidaemia, 1,466 (56%) hypertension, 686 (28%) were obese and 220 (9%) had T2DM. In the dataset, 1105 (42%) patients had a PCa progression event and 523 (20%) had died, including 411 from PCa.

471 patients (18%) fulfilled the criteria for CMA. Of those with CMA, 460 (99%) had low HDL, 454 (96%) hypertension, 408 (87%) were obese and 157(33%) had T2DM. There were 1,017 PCa progression, 1,005 PSA progression, 192 local progression and 501 metastatic progression events. Using Cox proportional hazards regression analysis, no evidence of an association was observed between baseline CMA and PCa progression (HR: 0.97, 95% CI: 0.82-1.14) or for any of the individual metabolic aberrations (**Table 26**). However, presence of CMA was associated with a worsening of time to local progression (HR: 1.61, 95% CI: 1.09-2.36) (**Table 27**). No evidence of a difference was observed between any of the individual metabolic aberrations and time to local progression, though a trend with low HDL levels was observed (HR: 1.65, 95%CI: 0.92-2.98). No difference was observed between the individual metabolic aberrations and time to metastatic progression, though a trend was noted for those with CMA (HR: 1.23, 95% CI: 0.96-1.57) (**Table 27**). No difference was observed in OS or PCSD in those with and without baseline metabolic aberrations or CMA (**Table 28**). A stratified analysis according to metastatic status at randomisation was performed (**Table 29**). A worsening of time to local progression in those with CMA was only seen for those who already had metastatic disease at randomisation (HR: 1.66, 95%CI: 1.08-2.55). However, the p value for the interaction test was p= 0.1102, therefore there was no statistically significant interaction seen.

Table 27: Baseline characteristics of men with locally advanced / metastatic PCa treated with ADT in the STAMPEDE study

Population Characteristic	Total n= 2,622 (SD)	No CMA[1] n = 2,151 (SD)	CMA[1] n= 471 (SD)
Age (years)			
Median (IQR)	67(10)	67(10)	67 (10)
Range	37-84	39-84	37-84
PSA pre-ADT (ng/L)			
Median (IQR)	62 (154)	62 (175)	56 (115)
Range	0-20590	0-20590	0-8760
Median F/U time (months)	21	20	20
Mean (SD)			
BMI (kg/m^2)	28.17 (6.60)	26.94 (6.32)	33.40 (5.06)
SBP (mmHg)	141.50 (18.20)	140.52 (18.18)	145.76 (17.69)
DBP (mmHg)	82.37 (27.66)	82.03 (25.59)	83.81 (35.25)
HDL (mmol/L)	1.52 (2.06)	1.61 (2.32)	1.23 (0.35)
Frequency (%)			
Smokers	323 (13)	293(14)	30(6)
Non Smokers	2196 (87)	1762 (86)	439 (93)
Missing	98	98	98
Staging at randomisation:			
T0	8 (<1)	8 (<1)	0 (0)
T1	32 (1)	28 (1)	4 (<1)
T2	214 (8)	160 (7)	54 (11)
T3	1740 (66)	1435 (67)	305 (65)
T4	474 (18)	398 (18)	76 (16)
TX	154 (6)	122 (6)	32 (7)
N0	1307 (50)	1067 (50)	240 (51)
N1	1195 (46)	986 (46)	209 (44)

NX	120 (4)	98 (4)	22 (4)
M0	1109 (42)	909 (42)	200 (42)
M1	1513 (58)	1242 (58)	271 (58)
Gleason sum score:			
≤7	546 (21)	457 (21)	89 (19)
8-10	1890 (72)	1529 (71)	361 (77)
Missing	186 (7)	165 (8)	21 (4)
Hormonal treatment at randomisation:			
Bicalutamide	19 (<1)	16 (<1)	3 (<1)
GnRH[2]	2603 (98)	2119 (98)	465 (99)
Maximum androgen blockade	8 (<1)	8 (<1)	0 (0)
Orchiectomy	11 (<1)	8 (<1)	3 (<1)
Metabolic Disturbance:			
Hypertension	1466 (56)	1012 (47)	454 (96)
Diabetes	220 (9)	63 (2)	157 (33)
Obesity	686 (28)	278 (14)	408 (87)
Low HDL[3]	1844 (87)	1384 (83)	460 (99)

[1] composite metabolic aberrations
[2] gonadotropin releasing hormone
[3] high density lipoprotein

Table 28: Hazard ratios for prostate cancer progression free survival for men with baseline metabolic aberrations compared to those without (N=2622) in the STAMPEDE study

Multivariate Analysis[1]		
	HR[4]	**95% CI**
CMA[2]	0.97	0.82-1.14
HBP	1.05	0.93-1.19
Obesity	0.96	0.83-1.11
HDL[3]	0.98	0.80-1.20
DM	0.94	0.74-1.19

[1] adjusted for age, Gleason sum score, PSA pre-ADT, type of ADT and TNM stage.
[2] composite metabolic aberrations
[3] high density lipoprotein
[4]HR >1 means worsened time to event

Table 29: Hazard ratios for time to PSA, local and metastatic progression for men with baseline metabolic aberrations compared to those without in the STAMPEDE study

Multivariate Analysis[1]		
	HR[4]	**95% CI**
PSA Progression		
CMA[2]	0.94	0.80-1.11
Hypertension	1.02	0.90-1.16
Obesity	0.96	0.83-1.11
Low HDL[3]	0.98	0.80-1.21
Diabetes Mellitus	0.96	0.76-1.22
Local progression		
CMA[2]	1.61	1.09-2.36
Hypertension	1.07	0.79-1.44
Obesity	1.1	0.82-1.63
Low HDL[3]	1.65	0.92-2.98
Diabetes Mellitus	1.11	0.59-2.09
Metastatic Progression		
CMA[2]	1.23	0.96-1.57
Hypertension	1.05	0.88-1.26
Obesity	1	0.81-1.22
Low HDL[3]	1.12	0.83-1.52
Diabetes Mellitus	1.06	0.74-1.51

[1] adjusted for age, Gleason sum score, PSA pre-ADT, type of ADT and TNM stage.
[2] composite metabolic aberrations
[3] high density lipoprotein
[4] HR >1 means worsened time to event

Table 30: Hazard ratios for time to all cause death and prostate cancer-specific death for men with baseline metabolic aberrations compared to those without in the STAMPEDE study

Multivariate Analysis[1]		
	HR[4]	**95% CI**
All-cause death		
CMA[2]	0.73	0.38-1.40
HBP	0.99	0.82-1.19
Obesity	1.02	0.60-1.72
HDL[3]	1.94	0.70-5.40
DM	1.21	0.55-2.66
Prostate Cancer Specific Death		
CMA[2]	0.86	0.38-1.97
HBP	0.95	0.77-1.18
Obesity	1.17	0.59-2.33
HDL[3]	1.23	0.37-4.11
DM	0.98	0.30-3.22

[1] adjusted for age, Gleason sum, PSA pre-ADT, type of ADT and TNM stage.
[2] composite metabolic aberrations
[3] high density lipoprotein
[4] HR >1 means worsened time to event

Table 31: Multivariate Hazard ratios for time to PSA, local and metastatic progression for men with baseline metabolic aberrations by metastatic status at randomisation into the trial in the STAMPEDE study

	Metastatic disease at randomisation n=1,509			Non metastatic disease at randomisation n=1,108		
	Event No	**HR[3]**	**95% CI**	**Event No**	**HR[3]**	**95% CI**
PSA Progression						
CMA[1]	784	0.95	0.79-1.15	221	1.01	0.72-1.43
HBP	784	0.97	0.84-1.11	221	1.21	0.92-1.60
Obesity	752	0.96	0.82-1.14	209	1.00	0.74-1.34
HDL[2]	631	1.07	0.84-1.36	180	0.81	0.54-1.22
DM	784	0.93	0.71-1.22	221	1.25	0.75-2.06
Local progression						
CMA[1]	146	1.66	1.08-2.55	46	0.90	0.39-2.09
HBP	146	1.12	0.80-1.59	46	0.84	0.44-1.61
Obesity	136	1.48	0.99-2.22	43	0.57	0.28-1.16
HDL[2]	111	1.31	0.66-2.59	36	7.31	1.62-32.98
DM	146	1.41	0.70-2.87	46	0.46	0.10-2.10
Metastatic Progression						
CMA[1]	428	1.26	0.97-1.64	73	1.11	0.57-2.14
HBP	428	1.08	0.89-1.31	73	0.96	0.59-1.57
Obesity	409	1.028	0.82-1.28	66	1.04	0.58-1.87
HDL[2]	345	1.159	0.82-1.63	61	0.96	0.44-2.06
DM	428	1.114	0.75-1.65	73	0.80	0.34-1.91

[1] composite metabolic aberrations
[2] high density lipoprotein
[3] HR >1 means increased risk of event

Discussion

This study investigated how baseline metabolic aberrations in men with localised/metastatic PCa treated with ADT affected outcomes of PCa progression, PCSD and death. No difference in PCa progression was observed for any of the individual baseline metabolic aberrations or those with CMA. However, when examining the different components of PCa progression, men with multiple metabolic aberrations at initiation of ADT, here referred to as CMA, had a worsening of local progression free survival, as compared to those without metabolic aberrations. In a further exploratory analysis, within subgroups defined by metastatic status, the difference in local progression was only observed in those men with metastatic disease at baseline; there was however no evidence of heterogeneity. Metabolic status was not reliably observed to be associated with any difference in OS or PCSD within this analysis, although the number of events is fairly modest.

A study using a smaller US cohort of 82 men with PCa treated with ADT previously reported an association between MetS and PSA progression on ADT and OS (86). They reported a worsening of time to PSA progression for patients with MetS, observing median times of 16 months vs. 36 months for men without MetS (p =0.003). The median OS for men with MetS was 36.5 months, compared with 46.7 months for those men without MetS (p=0.061) (**Figure 22**). The authors did not investigate an association with local or metastatic progression. A further recent study of 273 men with biochemically recurrent PCa following radical treatment, examined PCSD in men with baseline metabolic aberrations. The authors reported no association with PCSD, but did show that men with hypertension tended to have a higher cumulative incidence of PCSD compared to those without (HR: 1.59, 95% CI: 0.89-2.84). The authors also reported that men with MetS had a worsening of time to all-cause death (87).

There is biological plausibility that men with baseline metabolic aberrations may progress more rapidly than those without. MetS is known to be associated with low testosterone levels and testosterone replacement therapy has been associated with a significant reduction of fasting plasma glucose, triglycerides and waist circumference (193). PCa arising in a low testosterone environment is likely to be less sensitive to ADT and other hormonal treatments. Therefore, more rapid progression through these treatments could culminate in a worsening of PCa outcomes.

The findings of this study differ from those of Flanagan and colleagues (86) where an increased risk of PSA progression was observed. However, this study shows an association with local progression and a trend towards a worsening of time to metastatic progression. No difference for either time to PCSD or all cause death is shown. In contrast, Rudman et al (87) showed no association with PCSD, but they did report a worsening in time to all cause death. However, the median follow up time in this study was only 21 months vs. 11.6 years in that study. The short follow-up time may explain why a similar worsening in time to all cause death was not observed. Furthermore, these data were taken from a randomised controlled trial whereby participants were mandated to have a WHO performance status of 0-2, representing a selected group of those with better performance status and the least co-morbidities. It is clear that the association between metabolic aberrations and PCa outcomes is not a simple one. The conflicting results may occur due to the heterogeneity in study design and the populations used (194). The definitions of metabolic aberrations used and although broadly similar still results in some heterogeneity, largely in the lipid and glucose profiles used. This supports the need for prospective studies specifically investigating the association between MetS and PCa outcomes.

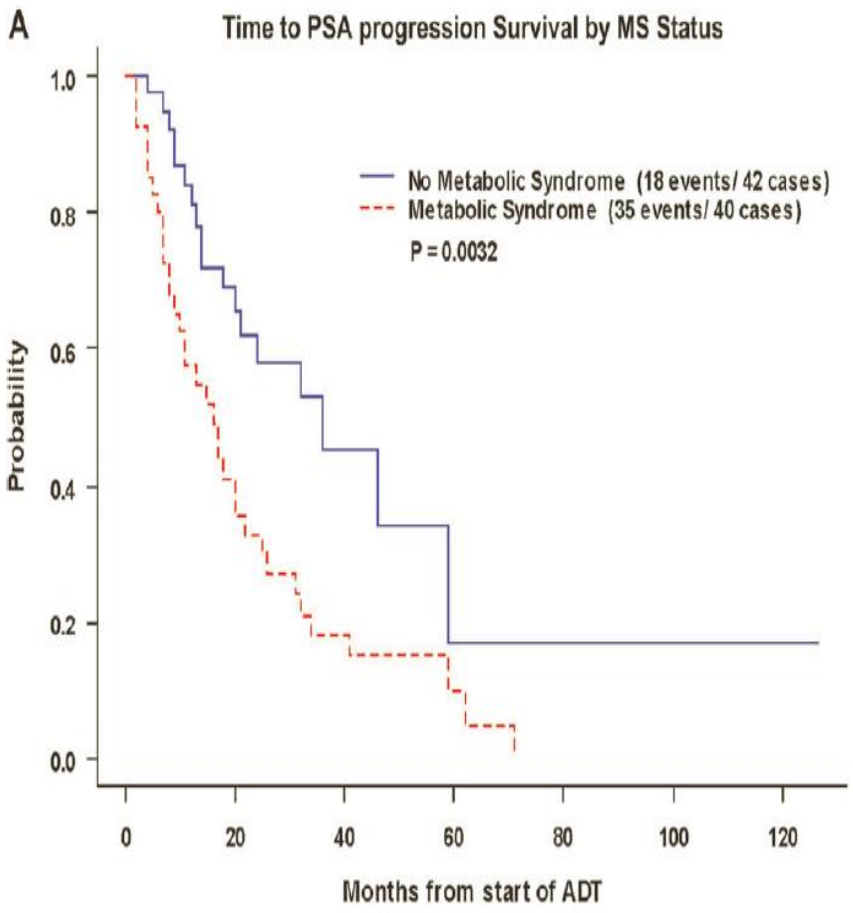
Strengths of this study are its large sample size and the quality of the data which was taken from STAMPEDE, an MRC randomised controlled trial. However, full metabolic profiles on patients, including waist hip ratios, full fasting lipids and glucose measurements were not routinely collected. Several previous studies have validated the use of BMI as a suitable surrogate marker for visceral obesity (195, 196). The absence of triglycerides and fasting glucose measurements in this study is a further limitation. Also, the use of patient reported co-morbidities, such as diabetes and hypertension, is not optimal, though they have been used in previous studies (87). Furthermore, another potential limitation of this work is that the first progression may be better reported than subsequent progressions e.g. local progression may be under reported by clinicians, in particular when PSA or metastatic progression occurs first. This potential underreporting needs to be considered when interpreting the data for local progression. A further limitation is that CMA may be induced by the ADT after randomisation and affect disease progression. Future studies will benefit from data on development of CMA during follow-up. Finally, the median follow-up time in this dataset was fairly short so that differences in PCa-specific and all cause death may not yet be identifiable. There is potential to repeat this analysis in the future once longer follow up has accrued.

Overall, this study highlights the need for further studies which collect full metabolic profiles prospectively, allowing longitudinal assessment of MetS as defined by the joint statement of major international associations. Since the most recent arm to open in STAMPEDE is examining the addition of metformin to standard of care, the protocol has been amended to allow prospective collection of a full metabolic profile at baseline, as well as serial measurements, allowing future analyses to address this important question (197).

Conclusion

The findings of this study suggest that the metabolic status of a man with PCa may be associated with certain poorer disease outcomes. Hence, by actively managing these metabolic risks it may be possible to improve these outcomes. Further longitudinal prospective studies examining this association are required to disentangle the role of MetS in PCa progression.

Figure 22: Time to PSA progression by metabolic syndrome status taken from paper by Flanagan et al (86)



Chapter VI: Metformin and Longevity Randomised Controlled Trial

Introduction

This chapter describes the Metformin and Longevity (METAL) trial, for which I wrote the protocol, all related study documents and gained all necessary approvals prior to its opening to recruitment in August 2015. My involvement has continued as both a sub-investigator and the trial coordinator. This chapter covers the background, rationale and design of the trial as well as an update on current progress and difficulties in running a 'window of opportunity' trial. The full trial protocol and summary of medicinal product characteristics (SMPC) for metformin are reproduced in **Appendix 5**. Recruitment to the trial is ongoing and so the analysis and results of the trial are not within the scope of this thesis. I have presented the protocol of the trial as a poster presentation at the annual conference of the ESMO in Copenhagen in 2016 and it has also been published in BMC Cancer, July 2017 (**Appendix 5**).

Background

The epidemiological evidence examining the association between metformin and PCa risk, mortality and outcomes is summarised in Chapter III. The biological mechanisms underlying these potential associations are not fully elucidated (198). One hypothesis is that its anti-neoplastic effect may be via an indirect effect of insulin lowering, which in turn leads to a reduction in IGF-1 levels. Both elevated insulin and IGF-1 levels are known to play a role in PCa development and progression (199). However, a host of direct molecular mechanisms has also been suggested. These are described below.

The potential direct molecular anti-cancer actions of metformin are summarised in **Figure 23** (200). Many of these actions are mediated via 5'-AMP- activated protein kinase (AMPK) (**Figure 24**). AMPK is an energy sensitising serine threonine kinase. It is made up of three subunits: alpha, beta and gamma. It is a crucial enzyme in cellular regulation, with important roles in gluconeogenesis, glucose homeostasis and lipid metabolism (201, 202). AMPK is activated under conditions of metabolic stress which leads to intracellular adenosine triphosphate (ATP) being depleted and AMP increasing. For AMPK to be fully activated, it requires phosphorylation of the alpha subunit. This is mediated by upstream kinases including LKB1 (**Figure 23/24**). Once activated, AMPK inhibits the mammalian target of rapamycin (mTOR) and other protein synthesis. These direct effects can

lead to reduced cell proliferation (203) and hence exert an anti-cancer effect. Metformin is a potent activator of AMPK via inhibition of complex I of the respiratory chain, which results in increased AMP (204).

Once activated, AMPK also inhibits important enzymes involved in lipogenesis, including Fatty acid synthase (FASN) and acetyl-CoA carboxylase (ACC). FASN is an enzyme which plays a role in the conversion of excess carbon into fatty acids for storage. It catalyses the conversion of precursors malonyl-CoA and acetyl-CoA into palmitate (**Figure 25**) and is implicated in carcinogenesis and has been shown to be upregulated in PCa (201). A hallmark of most cancer cells is an increase in *de novo* fatty acid synthesis and increased FASN expression has been linked to worse outcomes in PCa (205). Several pre-clinical studies have demonstrated that inhibition of FASN results in cell death in PCa cell lines (206).

It is suggested that metformin may also act via AMPK- independent mechanisms. These include inhibitory effects on extracellular signal–regulated kinases (ERK), nuclear factor kappa-B (NF-KB) and preventing tumour growth by preventing p53-induced autophagy (201).

Despite a wealth of preclinical work examining metformin's action on PCa, there is very limited data from human studies in PCa. A Canadian Phase 2 'window of opportunity' study evaluated the effects of metformin on PCa focusing on the AMPK pathway in paired pre-treatment and prostatectomy specimens (207). 22 patients of a planned 40, were given metformin in a dose escalation regimen from 500mg daily to 500mg three times per day prior to their prostatectomy. They had difficulties with recruitment and slow accrual and the trial was closed early due to these issues. The median duration of treatment was 41 days. Although the study was limited by small sample size and lack of a control arm, a change in the proliferation marker ki67 was observed following metformin therapy (mean 50% reduction). However, in this small study no change in pAMPK was observed. The study also demonstrated the safety and feasibility of metformin therapy in this patient group. To our knowledge this is the only clinical trial, with published results, which has specifically examined the molecular actions of metformin in the PCa patients.

Figure 23: Proposed molecular mechanisms of the anticancer effect of metformin (200)

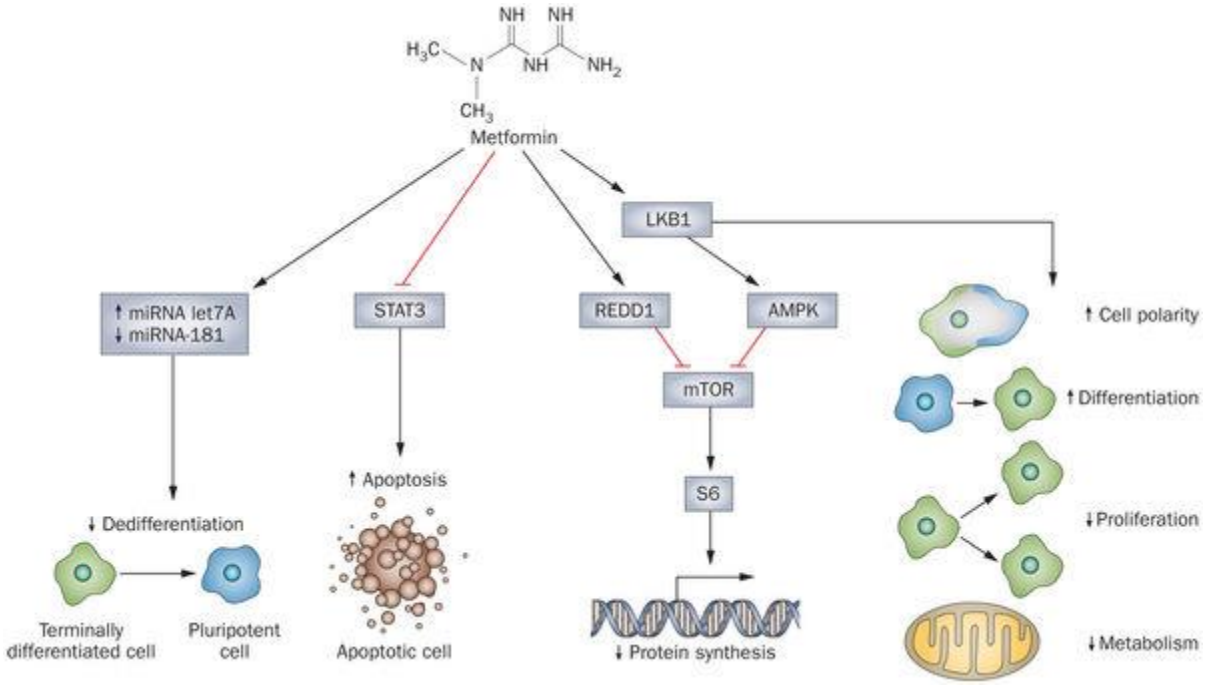


Figure 24: AMPK controls the main metabolic pathways in Prostate Cancer Cells (197)

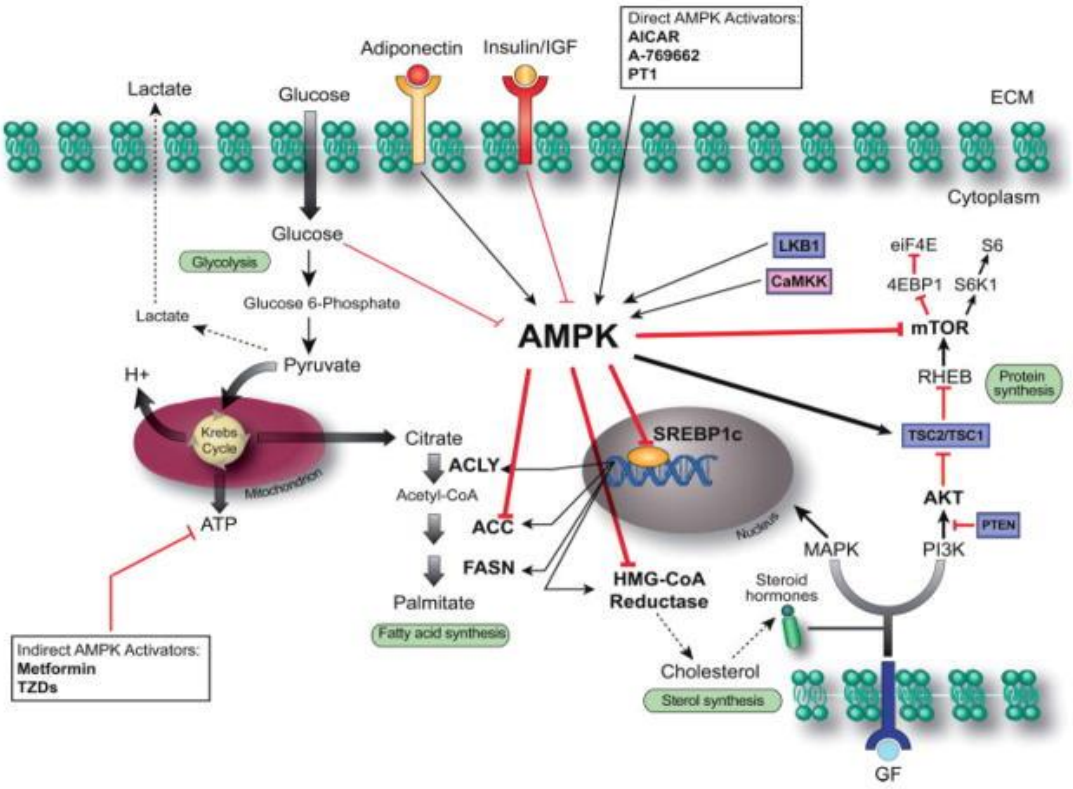
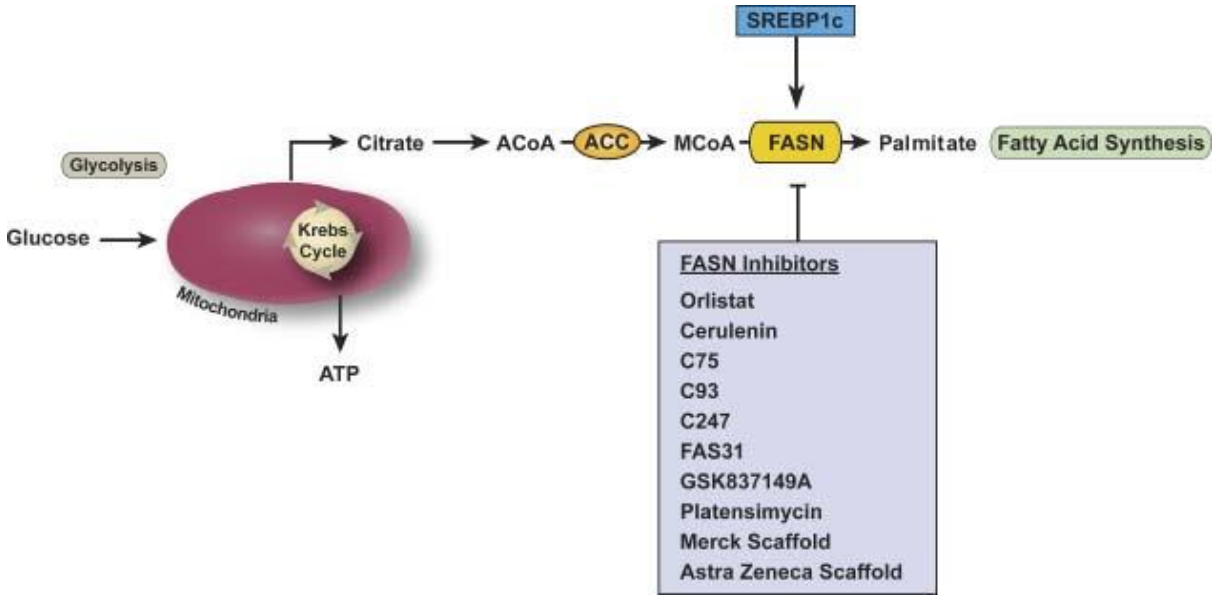


Figure 25: The central role of FASN in Fatty acid synthesis (197)



Rationale

A potential role for metformin in PCa has thus been suggested and given its wide availability, tolerable side effect profile and safety record it may represent a therapeutic option for men with PCa. However, as described above, the mechanism of action by which metformin exerts its anti-cancer effect has yet to be characterised. Thereby I designed a 'window of opportunity' trial that investigates this by comparing baseline prostate biopsies with post-treatment surgical specimens focussing on assessment of the FASN/AMPK axis. The study has a placebo arm in order to provide a control group.

Risk/benefits

The usual timing between diagnostic biopsy and prostatectomy is between four and six weeks, so participation in the study does not delay surgery. Since this is a proof of principle trial with a relative short duration of treatment, it is unlikely that patients will derive significant benefit by study participation. However, it has been shown that metformin is well tolerated in a non-diabetic population **(207)** and it is not anticipated that patients will experience increased morbidity by participating in the study.

Objectives and trial summary

METAL is a randomised, placebo-controlled, double-blind, window of opportunity study investigating the biological mechanism of metformin in PCa. Window of opportunity studies are designed to test one or more new treatments in the period between the patient's cancer diagnosis and them receiving their standard treatment. The treatment being received normally has curative intent, in this trial a radical prostatectomy, and the patients are therefore normally treatment naïve (208). Early stage patients eligible for prostatectomy were chosen, rather than later stage patients, as this study has a biological endpoint and requires tissue, which is not always available from patients with later stage disease.

100 non diabetic patients with newly-diagnosed, early stage PCa scheduled for radical prostatectomy will enter the main study and are randomised 1:1 to receive metformin (2g daily over 2 divided doses; Arm A) or placebo four weeks prior to prostatectomy (standard of care; Arm B). A subset of five patients (due to financial constraints) will enter the exploratory positron emission tomography–magnetic resonance imaging (PET-MRI) sub study. These five patients will all receive

metformin and will undergo an additional two PET-MRI Scans (see below). See **Figure 26** for the trial schema and **Figure 27** for the trial flow chart.

The trial objectives and primary, secondary and exploratory endpoints are summarised in **Table 30**. The primary objective of this study is to investigate the biological mechanism of metformin on PCa using pharmacodynamic markers. The primary endpoint for this study is therefore the difference in expression levels of biomarkers representing the FASN/AMPK pathway for the metformin and placebo groups, as measured by the H score.

Secondary endpoints include the difference in indicators of proliferation in the same groups, as well as differences in expression levels of the biomarkers between benign and malignant tissue (**Table 30**).

Following informed consent and screening, patients in the main study are randomised and continue metformin or placebo for four weeks until the evening prior to radical prostatectomy. In the event that surgery is scheduled for after this time point, patient will continue study drug for an additional one week.

Formalin fixed paraffin embedded tissue will be collected from baseline diagnostic biopsy and from the prostatectomy. Tissue will then be shipped to Centre for Molecular Oncologic Pathology (CMOP) at Dana Farber Cancer Institute (DFCI). The following analyses will be conducted at the CMOP on collected baseline and post-surgery tissue specimens:

- p-AMPK, p-ACC, FASN, ki-67 and Terminal deoxynucleotidyl transferase dUTP nick end labelling (TUNEL) will be assessed in benign and malignant tissue by immunohistochemistry using image analysis.
- The ki-67 proliferation index is assessed by point counting 1000 cells, and is reported as percent positive cells.

TUNEL is an apoptotic index defined as the number of apoptotic cells per 1000 tumour cells.
Remaining markers will be measured using a H-score. The H score is a way of quantifying the immunohistochemical staining of a section. Membrane staining is subjectively rated as an intensity (0, 1+, 2+, or 3+) which is determined for each cell in a fixed field. In one commonly used method, the percentage of cells at each staining intensity level is calculated, and finally, an H-score is assigned using the

following formula: [1 × (% cells 1+) + 2 × (% cells 2+) + 3 × (% cells 3+)]The final score ranges from 0 to 300. In this way more relative weight is given to higher-intensity membrane staining. The sample can then be considered positive or negative based on a pre-defined threshold (209). Methods for these analyses have been optimized and used in preliminary studies performed at CMOP. Tissue (prostate) metformin concentrations will also be performed. Details of these analyses lie outside of the scope of this thesis.

The primary endpoint of this study is pharmacodynamic and therefore time between study drug dose and prostatectomy is an important factor. To minimise the effects of dose reductions and interruptions, the primary endpoint analysis will be based on a per protocol analysis. Evaluable patients are defined as:

- Received at least 21 days (three weeks) of study drug between 1.5-2.0g daily.
- Received study drug uninterrupted for the last seven days prior to prostatectomy.

A secondary analysis will include an intention-to-treat analysis.

Following prostatectomy, all patients will be followed up for a final safety. Following this visit, patients do not require further study-related follow up and will continue to receive standard of care.

Exploratory Sub-study

The exploratory endpoint of this study involves ^{18}F Choline PET/MRI evaluation at baseline and post-metformin (pre-prostatectomy) for assessment of response in prostate tissue. Both PET and MRI are now well established in the diagnostic pathway for PCa (32) and there is a rationale for combining the two modalities to improve diagnostic accuracy, however this remains experimental at present (210, 211). This exploratory sub-study will include five patients with MRI positive disease, not randomised in the main trial, all of whom will receive metformin. Apart from the additional two visits for the ^{18}F Choline PET/MRI scans, they will follow the same trial protocol/ visit schedule as those in the main study (**Figure 27**). The criteria for enrolment in to this sub study are:

1. Patient willing to undergo two additional PET-MRI scans
2. MRI positive disease
3. Satisfactory completion of MRI safety questionnaire
4. Availability of ^{18}F Choline and scanning slots which would not result in a delay to the patient's enrolment into the study or to their surgery

No patients have yet been recruited to this sub study, recruitment is planned to begin in 2018.

Study setting

The trial is currently open at three tertiary referral hospitals in the UK.

- Guy's and St Thomas NHS Foundation Trust
- Royal Marsden NHS Foundation Trust
- Royal Gwent Hospital

Full details can be found on the EudraCT website https://www.clinicaltrialsregister.eu/ctr-search/search.

Eligibility Criteria

Inclusion Criteria:

Patients eligible to participate in this study are those who meet all of the following inclusion criteria:

1. Age 18 or older and willing and able to provide signed informed consent.
2. Histologically confirmed adenocarcinoma of the prostate, with a maximal tumour length of greater or equal to 6mm on core biopsy
3. No previous treatment for prostate cancer (including surgery, any hormone therapy, radiotherapy and cryotherapy)
4. Prostate biopsy within 6 months from screening
5. Radical prostatectomy is the scheduled treatment of choice
6. Eastern Cooperative Oncology Group (ECOG) Performance status less than or equal to 0 or 1
7. Adequate organ function, defined as follows:
   Haemoglobin >10.0g/dL
   Absolute neutrophil count >1.5x109/L
   Platelet count >100x109/L
   Renal function, eGFR >60ml/min (calculated by Cockcroft Gault)
   AST and/or ALT <2.5 x ULN
   Total Bilirubin <1.5 x ULN
8. Able to swallow the drug and comply with study requirements.

Exclusion Criteria:

Patients must NOT meet any of the following exclusion criteria:

1. Patients with a current or historical diagnosis of type one or two diabetes and/or have ever received metformin
2. Patients with hypersensitivity to any of the components of metformin or placebo tablet

3. History of or conditions associated with lactic acidosis such as shock or pulmonary insufficiency, alcoholism (acute or chronic), and conditions associated with hypoxaemia
4. Patients with chronic liver disease, severe cardiovascular impairment, cardiac failure, recent myocardial infarction, severe peripheral vascular disease or renal impairment (eGFR <60ml/min as measured by Cockcroft Gault)
5. Patients with acute severe disorders, for example infections with fever, pancreatitis, trauma, dehydration or reduced diet (<1000kcal or 4200kJ per day)
6. Other active malignancy over the last five years that has required systemic therapy, excluding:
    a. Adjuvant therapy in the curative setting
    b. Non-melanoma skin cancer
    c. Superficial transitional cell carcinoma (CIS-T1)
7. Current enrolment in an investigational drug or device study or participation in such a study within 30 days of signing consent.
8. Any subjects who is able to father a child and does not agree to use barrier protection, in the form of a condom, for the duration of the trial and for 16 weeks after the last study drug administration.

.

Sample size

The primary analysis for this study will quantify the difference in expression levels of biomarkers representing the FASN/AMPK pathway, as well as indicators of proliferation, for the metformin and placebo groups as measured by the H score using a simple two-sample t-test. Secondary analyses will include a comparison of differences in expression levels of biomarkers of the FASN/AMPK pathway, as well as indicators of proliferation, between benign and malignant tissue. Finally, we will perform a multivariate regression analysis to predict effects of metformin on expression levels using tumour and patient-specific characteristics.

Our original sample size calculation was based on the H-score used to assess expression levels of the studied biomarkers, which ranges from 0 to 300. We conducted a two-sided test (alpha=0.05; power=0.80) comparing the mean difference in the two groups for different scenarios as we will be testing different biomarkers. Based on these scenarios, we planned to recruit 90 patients for each

arm over a period of 15 months. However, since the start of the trial we have also identified other pathways to be studied in the prostate tissue. Moreover, we will set up a stratification trial following the biological information obtained in this trial. As a result we have reviewed our sample size calculation by increasing the type I error to 20% - which will require us to only recruit 50 men in each group. As we will conduct a follow-up trial with a clinical outcome, the potential type I error can be corrected for in this second trial. At the current stage it is thus more important to reduce the probability of failing to reject the null hypothesis when it is false. Hence, we have not changed the power in our revised sample size calculation. **Table 31** below shows the revised power calculation. In addition to the 50 patients in each arm, we will recruit an additional five patients in the exploratory endpoint group who will not be randomised.

Figure 26: METAL trial schema

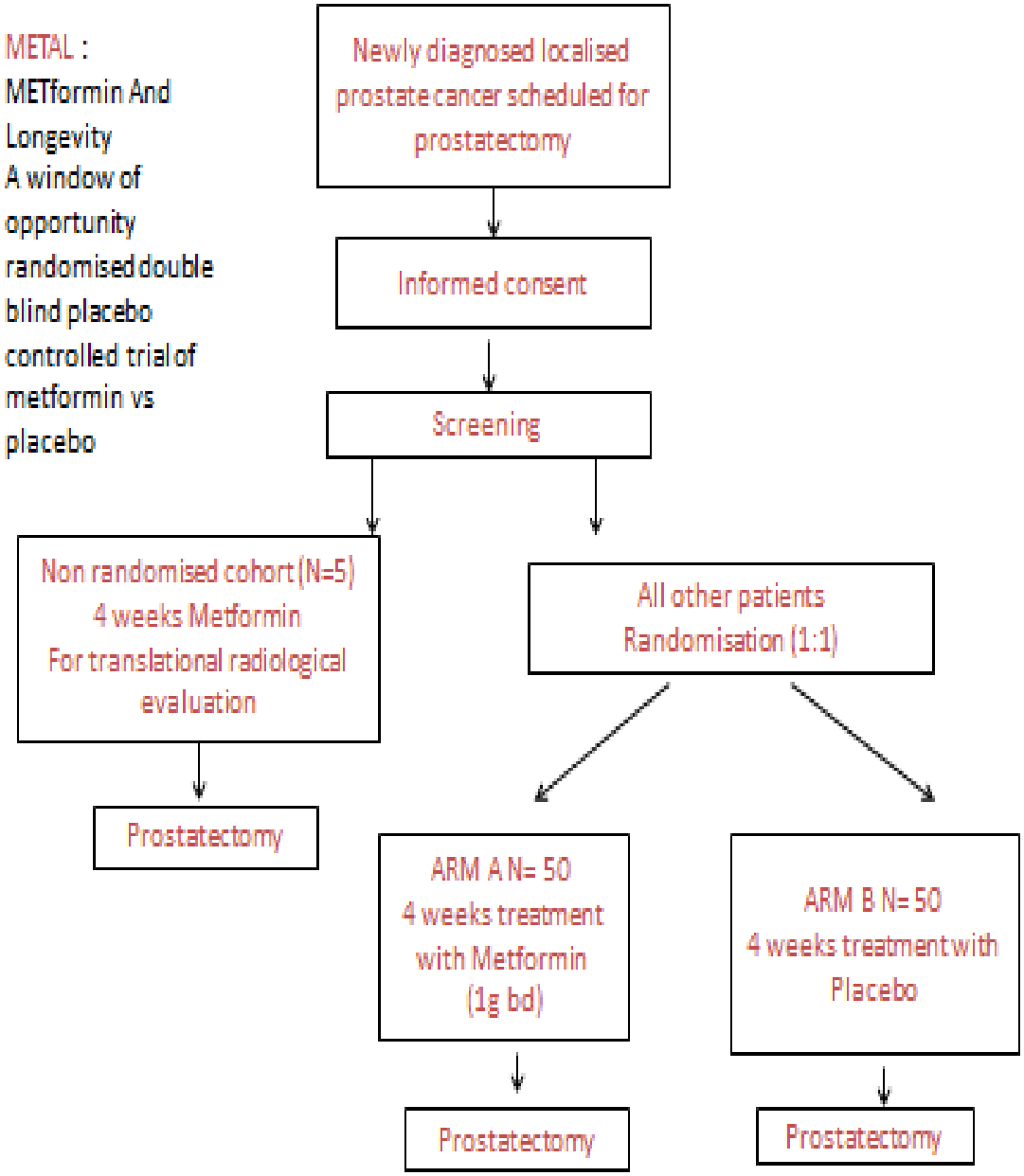


Figure 27: METAL trial flow chart

Phase	Screening	Pre-surgery Treatment			Surgery	Post-surgery
Time point	≤14 days before Baseline	Baseline Day 1 of treatment	Day 21 (+/- 2 days)	Day 28 (+/- 1 week) prior to surgery	Day 28 (+/- 1 week)	8-10[6]weeks post-op
Informed consent	X					
Eligibility review	X	X				
Randomisation		X				
Medical History[1]	X					
Demographics	X					
Physical Exam	X	X	x	x		x
Vital signs[2]	X		x	x		x
ECOG PS	X	X	x	x		x
Height	X					
Weight	X			x		x
Waist/Hip ratio	X			x		x
Haematology	X		x	x		x
Biochemistry[3]	X		x	x		x
Fasting Glucose/Lipids	X			x		
PSA and Testosterone	X			x		x
HbA1c	X					
Whole blood and Serum save[4]	X			X		
Study Drug Administration		X	x	x		
Medication review	X	X	x	x		x
Compliance evaluation (diary and verbal)			x	x		
Adverse events (CTCAE v4)[5]		X	x	x		x
Paraffin embedded tissue sent to laboratory	X				x	
Prostatectomy					x	
MRI safety assessment[7]	X					
^{18}F Choline PET/MRI[7]	X			X[5]		

1. Full medical history, including history other disease, active or resolved, concomitant illnesses and cancer diagnosis.
2. Blood pressure, pulse rate and oxygen saturation, BM
3. Renal profile, liver function tests, bone profile
4. To be taken at selected sites only and according to the Trial specific SOP
5. Clavien Dindo assessment to be completed at 8-10 weeks post operatively
6. This review will coincide with routine post-operative review
7. Only for the 5 subjects participating in the exploratory PET-MRI group

Table 32: METAL trial objectives and endpoints

Objectives	Endpoints
Primary endpoints	
To determine the biological effect of metformin on markers of the FASN/AMPK pathway in prostate tissue by comparison of pre and post-treatment samples.	Assessment of the difference in expression levels of markers of the FASN/AMPK pathway pre and post treatment between the placebo and metformin arms.
Secondary endpoints	
To evaluate the biological effect of metformin on markers of proliferation in prostate tissue by comparison of pre and post-treatment samples.	Assessment of the difference in expression levels of indicators of proliferation (ki67 and TUNEL) pre and post treatment between the placebo and metformin arms.
To evaluate differences in FASN/AMPK-associated markers in benign and malignant prostate tissue.	Assessment of the difference in expression levels of markers of the FASN/AMPK pathway and indicators of proliferation between benign and malignant prostate tissue in the placebo and metformin arms.
To measure metformin levels in prostate tissue.	Assessment of the difference in metformin levels in baseline and post-treatment prostate tissue.
To determine safety of metformin in this non-diabetic patient cohort.	Assessment of adverse events and laboratory evaluations.
To determine surgical toxicity.	Assessment of surgical-specific toxicities: time between biopsy and surgery, peri-operative bleeding, infection, rectal injury and length of hospital stay.
Exploratory Objectives and Endpoints	
To evaluate the effects of metformin on functional imaging of the prostate.	Difference in ^{18}F Choline PET/MRI between baseline and post-treatment (prior to prostatectomy) in a separate non-randomised cohort of five patients with MRI positive disease receiving metformin.

Table 33: Sample size calculation (two-sided test with power=0.80) to identify mean difference in H score between biopsy and radical prostatectomy specimen for the metformin and control group

	Mean Difference (SD) in Metformin Group	Mean Difference (SD) in Control Group	N needed with α=0.05	N needed with α=0.10	N needed with α=0.20
Scenario 1	15 (35)	0 (35)	86	38	50
Scenario 2	30 (65)	0 (65)	74	59	43
Scenario 3	20 (25)	5 (25)	44	35	26
Scenario 4	30 (50)	5 (50)	63	50	37

Trial progress and difficulties

Set up and opening

METAL is a Clinical Trial of Investigational Medicinal Product (CTIMP) and the set up and opening has followed a strict framework with well-established legal requirements and authorisations. The process is summarised in **Figure 28** below. I began work on the trial set up in October 2014. Working closely with all collaborators and investigators, I wrote the trial protocol (**Appendix 5**), laboratory manual, data management plan, case report form, patient information sheet, informed consent form and a compliance diary. I also worked with the PCa data manager to create a trial database using Microsoft Access. The trial was registered with EudraCT and clinicaltrials.gov. I successfully gained Research ethics committee (REC), Medicines and Healthcare products Regulatory Agency (MHRA), Administration Radioactive Substances Committee (ARSAC) and NHS Research and Development (R&D) approval. The study opened for recruitment at Guy's and St Thomas NHS Foundation Trust on 04/08/2015. The first patient was randomised on 01/09/2015.

Our first milestone (**Table 32**) was to finalise ethical and R&D approval and was due to be completed by March 2015. This was achieved, but with a 5 month delay. There were various reasons for this. REC approval was granted on the 31st March 2015 and MHRA approval on the 23rd March 2015. Each submission had recommended different minor alterations, so it was necessary to submit substantial amendments to both boards to combine the changes. Hence, final approval from both was not received until May 2015 due to amendments not being handled in the same time frame as initial applications. Concurrently, I had applied for local R&D approval in February 2015, but this was not received until May 2015. This constituted a major delay to opening. This was due partly to the delay with REC and MHRA approvals explained above. This was then further delayed by the amount of internal review boards through which it had to pass, some of which only meet monthly. Finally, once R&D approval had been issued on 18/06/2015, there was a further four week delay due to a problem in the pharmacy manufacturing unit. This resulted in the investigational medicinal product (IMP) not being ready and opening was hence delayed until the beginning of August.

Accrual and Duration of Study

The next milestone was the recruitment of 75 patients by October 2015. As described above, due to delays in the opening of the trial, the first patient was not recruited until 01/09/2015. The initial estimated accrual for the study was 10

patients a month. Allowing for a 5% drop out rate, patient accrual was expected to be completed within 18 months.

However, once open, recruitment has been substantially slower than predicted. **Figure 29** shows monthly recruitment at Guy's and St Thomas NHS Foundation trust from opening until August 2017. At the time of writing the trial had recruited a total of 40 patients across all sites. To August 2017 over 350 men had been screened as potential candidates for the trial. The reasons behind the slow recruitment are complex and multifactorial and have changed over time. Some of the particular issues encountered during recruitment to the METAL trial and actions taken to rectify them are summarised below:

1. Eligibility was limited to those with an original biopsy specimen at our site but this did not yield enough cases. An amendment was submitted to allow recruitment regardless of biopsy origin, allowing both local and tertiary referred patients to be recruited.
2. In order to be eligible the biopsy had to be within 8 weeks of consent. This was amended to 12 weeks and subsequently 6 months in further amendments. This allows both patients who defer surgery for personal reasons or those on AS who may not have had a recent biopsy, but have upgraded on MRI, to be recruited.
3. Further sites to boost recruitment have been added. King's College Hospital was added as a patient information site, so that patients seen there but whose surgery occurs at Guy's hospital can be approached. A second site at the Royal Marsden opened to recruitment in December 2015. However, due to a variety of staffing issues and competing trials, they have to date, only recruited two patients. Finally, a third site has opened to recruitment in September 2017 at the Royal Gwent hospital, Newport, Wales. At the time of writing they had yet to recruit their first patient.

The difficulties of recruiting to this kind of 'window of opportunity study' have been discussed elsewhere (208) and other trials with a similar design have also experienced problems with recruitment, some having to close early due to slow accrual (207). Whilst the benefits of this design of trial include the ability to test novel compounds in treatment naïve patients with access to pre and post treatment biopsy or surgical specimens, some of the weaknesses of this design, contribute directly to the recruitment difficulties which we have experienced. In this design, the

length of treatment is usually very short to avoid any delay to the proposed standard, definitive treatment which in most cases has curative intent. Due to this short duration and the testing of novel agents it is unlikely that individual participants will gain benefit from the intervention and hence makes it unethical to delay a patient's standard treatment to allow participation. This means that these trials are difficult to run logistically as time between diagnosis, treatment decision and definitive treatment can be short in many centres.

The future

Despite the difficulties in recruitment, all investigators remain committed to completing this important trial exploring the biological mechanisms by which metformin affects PCa, which still remain to be fully elucidated. Additional funding has been secured from the Guy's and St Thomas Hospital Charity to allow recruitment to continue for a further two years, until September 2019. The addition of a further site at the Royal Gwent and a push in recruitment at the Royal Marsden combined with continued steady recruitment at Guy's and St Thomas' mean that we are confident that recruitment to the trial can be completed.

Figure 28: Clinical Trials Roadmap - courtesy of KHP CTO

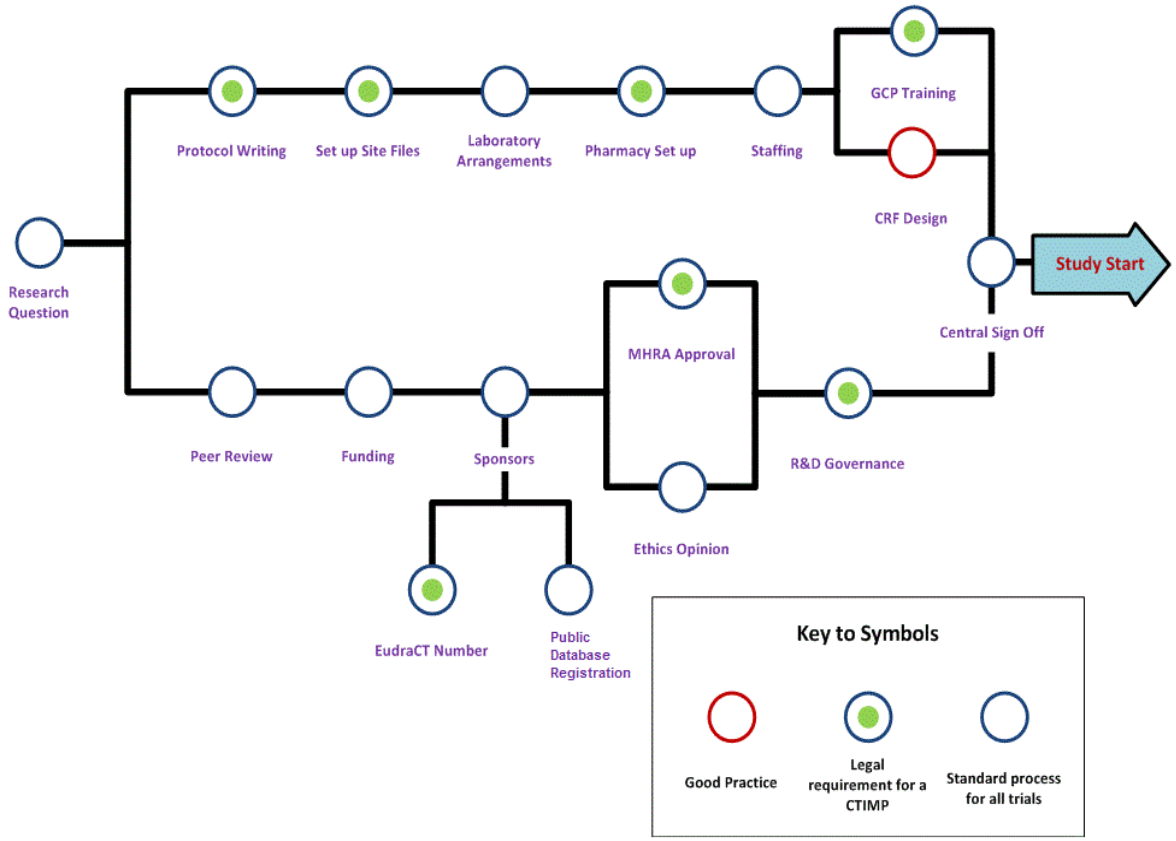


Figure 29: Monthly and total accrual to METAL trial at Guy's hospital

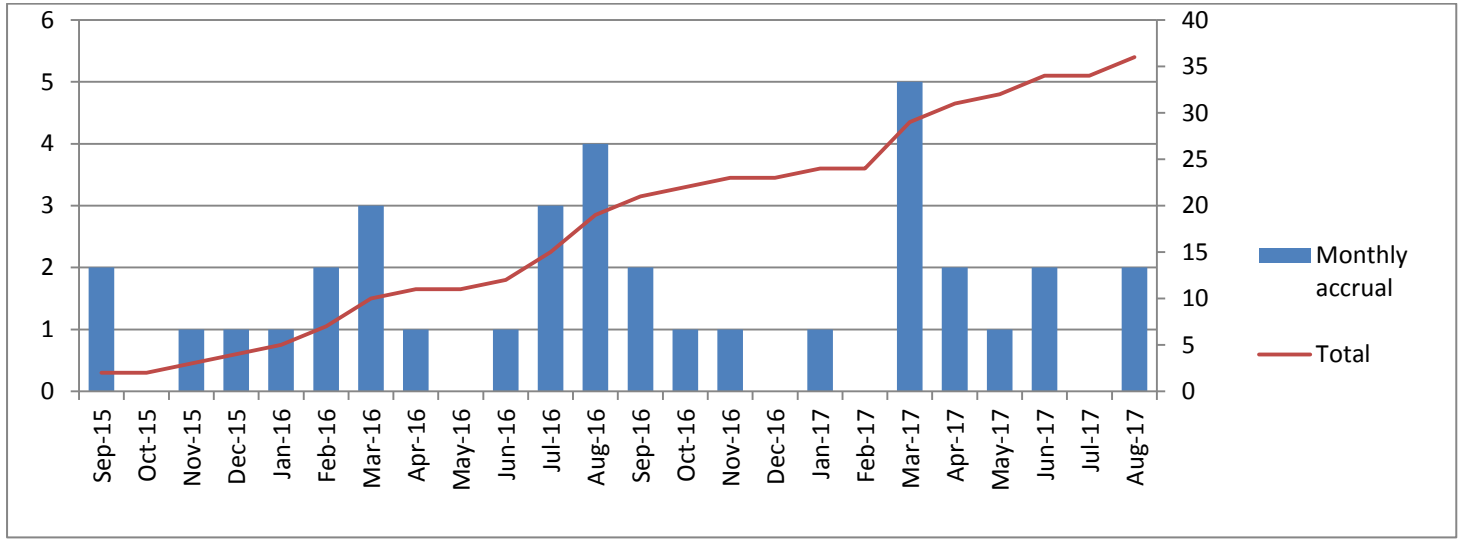


Table 34: Original milestones for the METAL trial

Milestone	March 2015	Oct 2015	Sep 2016
Finalise Ethical and R&D approval	X		
75 patients recruited and data/tissue before and after exposure collected		X	
Completion of tissue staining and comparison			X
Completion of analysis of PET/MRI scans for subset of patients			X
Complete statistical analysis of association between metformin and tissue markers			X
Complete statistical analysis of quality of life outcomes before and after exposure			X

Chapter VII: Final remarks and Future Direction

The prevalence of T2DM is rising worldwide and its onset is occurring earlier in patients' lives. This coupled with improvements in PCa survival ensures that the interplay between these two conditions will only become increasingly important in the years to come. Nevertheless, aspects of the relationship remain relatively little studied. This thesis serves to highlight this and hence can act as an outline for future research.

The explanation behind the inverse association reported in Chapter II between pre-existing T2DM and PCa incidence is far from clear. Further work within PCBaSe to explore potential explanations for this inverse association are now being planned including: a potential peak in PCa diagnostic activity around time of T2DM diagnosis, time since diagnosis of T2DM, age at time of DM diagnosis and PSA density in those with T2DM. I will apply for a lectureship to continue this work on the interaction between T2DM and PCa.

Furthermore, the impact of PCa on T2DM glycaemic control and management has not been widely studied. Further prospective studies in which the impact of both PCa and its treatments, are needed to corroborate the findings presented in Chapter IV of this thesis.

The impact of metabolic disturbances, including T2DM, on clinical outcomes in PCa also remains to be elucidated. Though early studies suggested that the presence of MetS had a negative effect on outcomes, such as time to PSA progression, subsequent work has failed to corroborate this. Further prospective studies with full baseline metabolic parameters and serial measurements throughout the treatment trajectory of men with PCa are needed. In light of the many new treatment options for PCa, it would also be interesting to assess the impact of a man's metabolic status on response to these treatments, both individually and also in the particular sequence in which they are received. As part of my lectureship application, I am therefore also planning further studies similar to the one presented in Chapter V, using data from the different treatment arms in the STAMPEDE trial including those treated with docetaxel chemotherapy and Abiraterone.

Finally, the mechanism of action of metformin in PCa is still unknown. To be able to use metformin most appropriately and potentially target patients who will gain the

most benefit from its use in the future, this fundamental understanding of its underlying mechanism of action will be paramount. The results of the METAL trial, once completed, should therefore help to guide future such stratification trials and research.

In conclusion, this thesis highlights the complexity of the interplay between T2DM and PCa, in which both conditions impact on both the treatment and disease outcomes of the other. Much of this interplay is still not fully understood and further research to fully characterise the different elements of the relationship is still needed.

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Appendix 1

Association between type 2 diabetes and curative treatment in men with intermediate and high risk localised prostate cancer

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Background/Objectives:

- Metabolic syndrome is defined as having 3 of the following :

- Metabolic conditions (diabetes, obesity or dyslipidaemia) have been linked with prostate cancer (PCa) aggressiveness and death.
- Prostate cancer (PCa) and Type 2 diabetes (T2DM) are increasingly prevalent conditions. They commonly occur together in the same patients .
- Little is known about how having T2DM influences receipt of curative treatment in localised PCa.
- **Here we investigated if curative PCa treatment was received less often by men with both PCa and T2DM.**

Materials and Methods:

- **Data from Prostate Cancer database Sweden (PCBaSe) from men with T2DM and PCa (n=2,210) was used to compare with those with PCa only (n=23,071).**
- All men with PCa had intermediate or high risk localised disease diagnosed between 1st January 2006 and 31st December 2014.
- Multivariate logistic regression was used to calculate odds ratios for receiving curative treatment in men with and without T2DM.
- Overall survival, up to 8 years of follow-up, was calculated for men with T2DM and PCa and also for men with T2DM alone from the PCa free comparison cohort within PCBaSe.

Conclusions:

- Men with T2DM were less likely to receive curative treatment for localised PCa.
- Men with T2DM and high risk PCa who did receive curative treatment had substantially higher survival compared to men with T2DM and PCa who were conservatively treated.
- Some of the survival differences represent a selection bias of the healthiest patients to receive curative treatment
- However, in men with conservatively treated high risk PCa, 22% died specifically of PCa, suggesting that a larger proportion of these men should have received curative treatment.

Results:

Table 1: Patient characteristics by diabetes status and diabetes treatment in PCBaSe

	No diabetes	%	T2DM[1] (all)	%	Insulin	%	Metformin	%
	n= 23071		n= 2210		n= 916		n= 1537	
Age, years								
<60	3016	13.1	134	6.1	55	6.0	94	6.1
60-64	4593	19.9	312	14.1	117	12.8	235	15.3
65-69	6184	26.8	611	27.6	266	29.0	451	29.3
70-74	5277	22.9	603	27.3	246	26.9	422	27.5
75-80	4001	17.3	550	24.9	232	25.3	335	21.8
CCI[2]								
0	18985	82.3	1512	68.4	558	60.9	1116	72.6
1	2428	10.5	383	17.3	183	20.0	245	15.9
2	1187	5.1	190	8.6	89	9.7	118	7.7
3+	471	2.0	125	5.7	86	9.4	58	3.8
Risk category[3]								
Intermediate risk	14503	62.9	1187	53.7	468	51.1	825	53.7
High risk	8568	37.1	1023	46.3	448	48.9	712	46.3
Educational level								
Low	7897	34.2	919	41.6	391	42.7	631	41.1
Middle	9091	39.4	854	38.6	355	38.8	597	38.8
High	5933	25.7	417	18.9	164	17.9	295	19.2
Missing	150	0.7	20	0.9	6	0.7	14	0.9
Civil status								
Not married	7241	31.4	779	35.2	332	36.2	551	35.8
Married	15830	68.6	1431	64.8	584	63.8	986	64.2
Gleason Score								
GS 2-6	4913	21.3	387	17.5	181	19.8	261	17.0
GS 7 (3+4)	9471	41.1	802	36.3	301	32.9	561	36.5
GS 7 (4+3)	4378	19.0	458	20.7	191	20.9	307	20.0
GS 7 UNS	162	0.7	14	0.6	4	0.4	10	0.7
GS 8	2627	11.4	334	15.1	143	15.6	238	15.5
GS 9-10	1520	6.6	215	9.7	96	10.5	160	10.4
Cores positive								
0-33%	8767	43.5	779	40.3	321	40.4	531	39.1
33-66%	7043	35.0	650	33.6	267	33.6	467	34.4
66-100%	4335	21.5	505	26.1	206	25.9	360	26.5
Serum PSA (ng/ml)								
0-3	418	1.9	52	2.5	23	2.6	32	2.2
3-10	10112	46.0	909	43.0	336	38.5	661	45.1
10-20	7605	34.6	706	33.4	313	35.9	478	32.6
20-50	3837	17.5	446	21.1	201	23.0	295	20.1
Primary Treatment								
ADT[4]	3552	15.4	560	25.3	276	30.1	336	21.9
Radical Prostatectomy	9057	39.3	501	22.7	182	19.9	377	24.5
Radiotherapy	6343	27.5	687	31.1	257	28.1	524	34.1
Watchful Waiting	4119	17.9	462	20.9	201	21.9	300	19.5

[1]Type 2 Diabetes
[2]Charlson Co-morbidity Index
[3]Risk groups according to modification of the National Comprehensive Cancer Network Practice Guidelines
[4] Androgen deprivation therapy

Table 2: Odds ratios and 95% confidence intervals of curative treatment by diabetes status.

	All men with diabetes		Insulin T2DM		Metformin T2DM	
Model	OR	95%CI	OR	95%CI	OR	95%CI
Diabetes	0.58	(0.53 - 0.63)	0.47	(0.41 - 0.53)	0.73	(0.66 - 0.81)
+ Age	0.73	(0.66 - 0.81)	0.55	(0.47 - 0.65)	0.87	(0.77 - 0.99)
+CCI	0.78	(0.70 - 0.86)	0.62	(0.53 - 0.72)	0.91	(0.81 - 1.03)
+T Stage	0.79	(0.71 - 0.88)	0.62	(0.53 - 0.73)	0.93	(0.82 - 1.05)
+Gleason	0.75	(0.67 - 0.83)	0.60	(0.51 - 0.71)	0.88	(0.77 - 0.99)
+PSA[2]	0.75	(0.67 - 0.83)	0.61	(0.51 - 0.71)	0.88	(0.77 - 1.00)
+% positive cores	0.74	(0.66 - 0.83)	0.59	(0.50 - 0.70)	0.87	(0.77 - 0.99)
+mode of detection	0.76	(0.68 - 0.84)	0.61	(0.51 - 0.72)	0.88	(0.78 - 1.01)
+Education	0.77	(0.69 - 0.86)	0.62	(0.52 - 0.73)	0.90	(0.79 - 1.02)
+Civil Status	0.78	(0.69 - 0.87)	0.62	(0.53 - 0.74)	0.91	(0.80 - 1.04)

Crude model is followed by multivariate models with increasing number of factors included as adjustment

[1]Calculated excluding diabetes
[2]For PSA linear splines with knots at 3, 10 and 20 were used

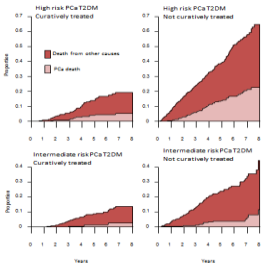

Figure 2: Cumulative incidence of prostate cancer death and death from other causes according to prostate cancer risk category and prostate cancer treatment

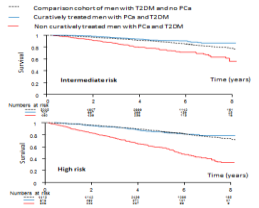

Figure 1: Overall survival for men with type 2 diabetes mellitus according to prostate cancer risk category and prostate cancer treatment.

Summary of Results:

- **Men with T2DM were less likely to receive curative treatment** for localized PCa (*OR 0.78 95% CI 0.69-0.87*) (Table 2).
- Men with T2DM treated with insulin were less likely to receive curative treatment (*OR: 0.62; 95%CI: 0.53-0.74*) than men on metformin (*OR: 0.91; 95%CI: 0.80-1.04*) (*Table 2*).
- At 8 years of follow-up, the survival was 73% for men with T2DM and no PCa, 79% for men with T2DM and high risk PCa who received curative treatment and 33% for men who did not (Figure 1).
- The cumulative incidence of PCa death was low when curative treatment was received. **But in high risk PCa not curatively treated the cumulative incidence of PCa death contributed to a much greater proportion of the overall death** (Figure 2).

Discussion points:

- Are clinicians undertreating men with T2DM ? If so is it appropriate?
- How do additional co-morbidities affect the receipt of curative treatment?

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Certificate

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D. Crawley

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Association between type 2 diabetes, curative treatment and survival in men with intermediate- and high-risk localized prostate cancer

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Objective

To investigate whether curative prostate cancer (PCa) treatment was received less often by men with both PCa and Type 2 diabetes mellitus (T2DM) as little is known about the influence of T2DM diagnosis on the receipt of such treatment in men with localized PCa.

Subjects and Methods

The Prostate Cancer database Sweden (PCBaSe) was used to obtain data on men with T2DM and PCa (n = 2210) for comparison with data on men with PCa only (n = 23 071). All men had intermediate- (T1–2, Gleason score 7 and/or prostate-specific antigen [PSA] 10–20 ng/mL) or high-risk (T3 and/or Gleason score 8–10 and/or PSA 20–50 ng/mL) localized PCa diagnosed between 1 January 2006 and 31 December 2014. Multivariate logistic regression was used to calculate the odds ratios (ORs) for receipt of curative treatment in men with and without T2DM. Overall survival, for up to 8 years of follow-up, was calculated both for men with T2DM only and for men with T2DM and PCa.

Results

Men with T2DM were less likely to receive curative treatment for PCa than men without T2DM (OR 0.78, 95% confidence interval 0.69–0.87). The 8-year overall survival rates were 79% and 33% for men with T2DM and high-risk PCa who did and did not receive curative treatment, respectively.

Conclusions

Men with T2DM were less likely to receive curative treatment for localized intermediate- and high-risk PCa. Men with T2DM and high-risk PCa who received curative treatment had substantially higher survival times than those who did not. Some of the survival differences represent a selection bias, whereby the healthiest patients received curative treatment. Clinicians should interpret this data carefully and ensure that individual patients with T2DM and PCa are not under- nor overtreated.

Keywords

diabetes, curative treatment, prostatectomy, external beam radiotherapy, #ProstateCancer, #PCSM

Introduction

Prostate cancer (PCa) is the most common cancer in men in Europe, with ~417 000 new cases diagnosed in 2012 [1]. Incidence is strongly related to age, and ~36% of cases are diagnosed in men aged ≥75 years, with a peak incidence at between age 75 and 79 years [2]. More than 60 million people have been diagnosed with type 2 diabetes mellitus (T2DM) across Europe, and it is estimated that >10% of men in Europe have T2DM [3]. As a result, these two increasingly prevalent conditions often occur together in the same men; however, the relationship is more complex than just two prevalent conditions co-existing. T2DM is included in the cluster of disorders that comprise metabolic syndrome [4]. During the last decade, studies have investigated whether metabolic syndrome is involved in the aetiology of PCa [5–7]. A meta-analysis to quantify the risk of PCa related to metabolic syndrome found a pooled relative risk of 1.54 (95%

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CI 1.23–1.94) [4]. Recent studies have also suggested that the presence of metabolic syndrome or some of its features is associated with higher-grade disease in men with PCa, and can lead to more rapid progression to castrate-resistant PCa [8,9].

Men with untreated localized PCa have different life expectancy depending on their comorbidities [10]. A Canadian case–cohort study of 630 men studied the impact of specific comorbid conditions on death within 10 years in men with localized PCa [11]. Respiratory and cardiovascular diseases (CVDs) were the most common conditions and were most strongly associated with an increased risk of death. Pharmacologically treated T2DM was present in 7% of the men at the time of PCa diagnosis and was associated with a 35% higher risk of death from other causes than PCa at 10 years. The association between components of the Charlson comorbidity index (CCI) on mortality after radical prostatectomy (RP) has also been studied. Eight conditions were significant predictors of overall mortality, including diabetes [12]. T2DM may therefore be associated with a shorter life expectancy in men with PCa.

As a result of the association between comorbidities and life expectancy in men with localized PCa [10,12,13], current PCa treatment guidelines recommend that a man should have a life expectancy of ≥10 years in order for curative treatment to be indicated [14].

Given the above, we used data from PCBaSe Sweden to investigate if a diagnosis of T2DM decreased the probability of curative treatment in men with localized PCa and how this was associated with PCa-specific and all-cause mortality.

Study Population and Methods

Study Population and Data Collection

PCBaSe Sweden 3.0 is based on the National Prostate Cancer Register of Sweden (NPCR), which became nationwide in 1998 and covers 98% of all newly diagnosed cases of PCa, as compared with the Swedish Cancer Register [15,16]. The NPCR includes information on date of diagnosis, age at diagnosis, tumour stage and differentiation, and serum levels of PSA at time of diagnosis. Risk categories were determined according to a modified version of the National Comprehensive Cancer Network guidelines [17] as follows: low risk: local clinical stage T1–2, Gleason score 2–6 and PSA <10 ng/mL; intermediate risk: T1–2, Gleason score 7 and/or PSA 10–20 ng/mL; high risk: T3 and/or Gleason score 8–10 and/or PSA 20–50 ng/mL; regionally metastatic/locally advanced: T4 and/or N1 and/or PSA 50–100 ng/mL in the absence of distant metastases (M0 or MX); and distant metastases: M1 and/or PSA >100 ng/mL. Using the Swedish personal identity number, five PCa-free men from the general population in Sweden were randomly selected within sets of men who matched each index case on birth year and county of residence, and were included in a PCa-free control cohort [15]. Both men with PCa and those in the control cohort were subsequently linked to a series of national healthcare registers and demographic databases, to obtain data on comorbidity, socio-economic status, and cause of death, including the National Diabetes Register.

PCBaSe^{traject} includes all of the data in PCBaSe 3.0, but has additional linkages. It focuses specifically on men diagnosed with PCa between 1992 and 2012 with available information on their complete treatment trajectory [16]. For the present study, we included all men diagnosed with intermediate- or high-risk localized PCa (i.e. eligible for radical treatment with either RP or radiotherapy [RT]) between 1 January 2006 and 31 December 2014, to allow use of the National Prescribed Drug Register which started on 1 July 2005. The Regional Research Ethics Board at Umeå University approved the present study.

The main outcome variable for this study, treatment with RP and RT, was retrieved from PCBaSe^{traject}, which represents actual treatment received, not just intended primary treatment. We looked only at primary treatment, i.e. first definitive treatment received after PCa diagnosis, and not subsequent treatments. The main exposure variable for the present study, T2DM, was defined as receiving two or more consecutive prescriptions for an antidiabetic drug within 6 months. Information on filled prescriptions of metformin, sulphonylurea and insulin was obtained from the National Prescribed Drug Register using Anatomical Therapeutic Chemical (ATC) classification codes (insulin: ANA; metformin: A10BA/BD; sulphonylurea:A10BB) [18]. Fewer than 2% of those with T2DM received prescriptions for alternative oral hypoglycaemic drugs; in the present analysis these people were considered in the metformin group. We did not exclude those with type 1 diabetes receiving insulin prescriptions, however, these cases were few. Comorbidities were measured according to the CCI, which assigns weights to a number of medical conditions, including diabetes and hypertension, based on discharge diagnoses in the Patient Register [13]. We excluded diabetes from the CCI score. Each condition was assigned a score of 1, 2, 3 or 6, and the final CCI was the sum of these scores. Individuals were grouped into CCI categories for final scores of 0, 1, 2 or ≥3. Information on age at diagnosis, T stage, Gleason score, PSA at diagnosis, proportion of cores with cancer, mode of detection of PCa, education and marital status was also used. For men with missing data on Gleason score (0.7%), we applied multivariate imputation using chained equations (MICE), also known as imputation, using fully conditional specifications [19]. The MICE method imputes multiple variables sequentially using univariate fully conditional specifications.

Analysis

We used multivariate logistic regression to calculate odds ratios (ORs) for receiving curative treatment in men with and without T2DM (as defined above). The analysis was adjusted for age, T-stage, Gleason score, proportion of cores with cancer, CCI (excluding diabetes), mode of detection, education and marital status. When adjusting for PSA, linear splines with knots at 3, 10 and 20 were used.

We then performed an analysis to evaluate how an additional diagnosis of hypertension, dyslipidaemia or CVD, as compared with only T2DM, affected the association between T2DM and curative treatment. We used ATC codes for the following prescriptions from the Prescribed Drug Register to assess these additional diagnoses: statins (C10), anti-hypertensive medication (C02) and anti-coagulants (B01).

To evaluate the association of PCa and T2DM with survival, we created a comparison cohort including men with only T2DM from the PCa-free cohort. First, we selected all index cases (PCa and T2DM, as registered with a date of diagnosis from the National Diabetes Register). Controls in the comparison cohort were matched with these index cases on age (± 1 year), duration of T2DM and type of T2DM treatment (insulin vs oral drugs). For each index case we selected five control subjects in each comparison cohort. Overall survival for up to 8 years of follow-up was then calculated for men in the comparison cohort and for men with T2DM and PCa who did and did not receive curative treatment. The 8-year survival probabilities were assessed because data were only available for the period 2006–2014. Finally, we calculated the cumulative incidence of PCa-specific death and death from other causes in those who did and did not receive curative treatment.

All data management was performed with SAS version 9.3 (SAS Institute, Cary, NC, USA) and all data analysis was conducted using R version 2.13.2 (R Foundation for Statistical Computing, Vienna, Austria).

Results

A total of 2210 men with PCa and T2DM and 23 071 men with PCa only were included in the analysis. Of those with T2DM, 916 were treated with insulin and 1537 with metformin (Table 1). Men with T2DM were older than those without T2DM; only 6% of men with T2DM were aged <60 years, compared with 13% of men with no diabetes (Table 1). Men with T2DM also had a higher CCI score and were more likely to have high-risk than intermediate-risk PCA than men without T2DM (Table 1). Those with T2DM were also more likely to have a Gleason score >8, a higher proportion of cores with cancer and PSA >20 ng/mL (Table 1).

Men with both T2DM and PCa were less likely to receive curative treatment for PCa than those without T2DM (OR 0.78; 95% CI 0.69–0.87 [Table 2]). Men with T2DM treated with insulin were less likely to receive curative treatment (OR 0.62; 95% CI 0.53–0.74) than men on metformin (OR 0.91; 95% CI 0.80–1.04 [Table 2]).

Men with other comorbidities (based on additional filled prescriptions for drugs for hypertension, dyslipidaemia or CVD) in addition to T2DM had virtually the same probability of curative treatment for PCa: men with T2DM only (OR 0.78; 95% CI 0.69–0.88), men with T2DM and dyslipidaemia (OR 0.79; 95% CI 0.69–0.90), and men with T2DM and CVD (OR 0.75; 95% CI 0.60–0.93 [Table 3]).

The 8-year overall survival was lower in PCa-free men with T2DM compared with men with T2DM and PCa who received curative treatment. At 8-year follow-up, the survival was 73% for men with T2DM and no PCa, 79% for men with T2DM and high-risk PCa who received curative treatment, and 33% for men with T2DM and high-risk PCa who did not receive curative treatment (Fig. 1). The corresponding survival rates for intermediate-risk PCa were 77%, 86% and 55%. The cumulative incidence of death from PCa was low in both intermediate- and high-risk PCa groups when curative treatment was received. In men with intermediate-risk PCa who were not curatively treated, the cumulative incidence of PCa-specific death remained low at 8-year follow-up, whilst the cumulative incidence of death from other causes was much higher; however, in men with high-risk PCa, the cumulative incidence of PCa-specific death contributed to a much greater proportion of the overall death rate in those not treated curatively (Fig. 2).

Discussion

Men with T2DM were less likely to receive curative treatment for localized PCa, particularly those receiving insulin. While men with T2DM and high-risk PCa who did receive curative treatment had a substantially higher survival rate than men with T2DM and PCa who were conservatively treated, those selected for curative treatment were found to be the healthiest patients.

Comorbidities affect 10-year mortality more than PCa-specific mortality in men with conservatively treated localized PCa [10–12], which has led to the recommendation that men have a life expectancy of ≥10 years in order for curative treatment to be indicated [14]. It is difficult to predict an individual's 10-year life expectancy, however, and none of the existing nomograms that help calculate this are currently widely used in clinical practice [20].

The impact of comorbidity and age on treatment and survival in men with PCa has been investigated in a Dutch study of >6000 men [21]. The proportion of men aged 60–69 years

Table 1 Patient characteristics by diabetes status and diabetes treatment recorded in the Prostate Cancer database Sweden (PCBaSe).

	No diabetes (*N* = 23071)		T2DM (all; *N* = 2210)		Insulin (*N* = 916)		Metformin (*n* = 1537)	
Mean age at PCa diagnosis, years	67.9		70		70.1		69.6	
	n	%	*n*	%	*n*	%	*n*	%
Age								
<60 years	3016	13.1	134	6.1	55	6.0	94	6.1
60–64 years	4593	19.9	312	14.1	117	12.8	235	15.3
65–69 years	6184	26.8	611	27.6	266	29.0	451	29.3
70–74 years	5277	22.9	603	27.3	246	26.9	422	27.5
75–80 years	4001	17.3	550	24.9	232	25.3	335	21.8
Year of PCa diagnosis								
2006–2008	7843	34.0	672	30.4	276	30.1	441	28.7
2009–2010	8006	34.7	751	34.0	321	35.0	511	33.2
2011–2012	7222	31.3	787	35.6	319	34.8	585	38.1
CCI								
0	18985	82.3	1512	68.4	558	60.9	1116	72.6
1	2428	10.5	383	17.3	183	20.0	245	15.9
2	1187	5.1	190	8.6	89	9.7	118	7.7
≥3	471	2.0	125	5.7	86	9.4	58	3.8
Risk category*								
Intermediate	14503	62.9	1187	53.7	468	51.1	825	53.7
High	8568	37.1	1023	46.3	448	48.9	712	46.3
Educational level								
Low	7897	34.2	919	41.6	391	42.7	631	41.1
Middle	9091	39.4	854	38.6	355	38.8	597	38.8
High	5933	25.7	417	18.9	164	17.9	295	19.2
Missing	150	0.7	20	0.9	6	0.7	14	0.9
Marital status								
Not married	7241	31.4	779	35.2	332	36.2	551	35.8
Married	15830	68.6	1431	64.8	584	63.8	986	64.2
Gleason score								
2–6	4913	21.3	387	17.5	181	19.8	261	17.0
7 (3 + 4)	9471	41.1	802	36.3	301	32.9	561	36.5
7 (4 + 3)	4378	19.0	458	20.7	191	20.9	307	20.0
7 Unspecified	162	0.7	14	0.6	4	0.4	10	0.7
8	2627	11.4	334	15.1	143	15.6	238	15.5
9–10	1520	6.6	215	9.7	96	10.5	160	10.4
Cores positive for cancer								
0–33%	8767	43.5	779	40.3	321	40.4	531	39.1
33–66%	7043	35.0	650	33.6	267	33.6	467	34.4
66–100%	4335	21.5	505	26.1	206	25.9	360	26.5
Serum PSA								
0–3 ng/mL	418	1.9	52	2.5	23	2.6	32	2.2
3–10 ng/mL	10112	46.0	909	43.0	336	38.5	661	45.1
10–20 ng/mL	7605	34.6	706	33.4	313	35.9	478	32.6
20–50 ng/mL	3837	17.5	446	21.1	201	23.0	295	20.1
Primary treatment								
ADT	3552	15.4	560	25.3	276	30.1	336	21.9
RP	9057	39.3	501	22.7	182	19.9	377	24.5
RT	6343	27.5	687	31.1	257	28.1	524	34.1
Watchful waiting	4119	17.9	462	20.9	201	21.9	300	19.5

*ADT, androgen deprivation therapy; CCI, Charlson comorbidity index; PCa, prostate cancer; RP, radical prostatectomy; RT, radiotherapy; T2DM, type 2 diabetes mellitus. *Risk groups according to modification of the National Comprehensive Cancer Network Practice Guidelines [17].*

who underwent RP decreased significantly, from 32% of men without comorbidity to 17% of men with two or more comorbid conditions. This proportion decreased further, from 8% to 3%, in those aged 70–79 years. A previous study using data from PCBaSe showed that as CCI score increased, men were more likely to receive RT than RP [22]. The present study findings are in line with these observations, even after taking into account a wide range of potential confounders (age, comorbidities and cancer characteristics).

Nevertheless, to interpret the present findings, it is important to evaluate life expectancy as outlined in the guidelines for PCa treatment [14]. The life expectancy of a Swedish man at age 65 is 19 years [23], with similar figures seen across Europe [23]. T2DM decreases life expectancy by up to 10 years [24]; however, men with PCa and T2DM who received curative treatment in the present study had substantially higher overall survival rates than men with T2DM and PCa who received conservative treatment. The

Table 2 Odds ratios and 95% CIs for curative treatment by diabetes status.

	All men with diabetes		Insulin T2DM		Metformin T2DM	
Model	**OR**	**95%CI**	**OR**	**95%CI**	**OR**	**95%CI**
Diabetes	0.58	0.53–0.63	0.47	0.41–0.53	0.73	0.66–0.81
+ Age	0.73	0.66–0.81	0.55	0.47–0.65	0.87	0.77–0.99
+CCI*	0.78	0.70–0.86	0.62	0.53–0.72	0.91	0.81–1.03
+T stage	0.79	0.71–0.88	0.62	0.53–0.73	0.93	0.82–1.05
+Gleason	0.75	0.67–0.83	0.60	0.51–0.71	0.88	0.77–0.99
+PSA level†	0.75	0.67–0.83	0.61	0.51–0.71	0.88	0.77–1.00
+% positive cores	0.74	0.66–0.83	0.59	0.50–0.70	0.87	0.77–0.99
+mode of detection	0.76	0.68–0.84	0.61	0.51–0.72	0.88	0.78–1.01
+Education	0.77	0.69–0.86	0.62	0.52–0.73	0.90	0.79–1.02
+Marital status	0.78	0.69–0.87	0.62	0.53–0.74	0.91	0.80–1.04

*CCI, Charlson comorbidity index; OR, odds ratio; T2DM, type 2 diabetes mellitus. Crude model is followed by multivariate models, with increasing number of factors included as adjustment. *Calculated excluding diabetes. †For PSA, linear splines with knots at 3, 10 and 20 were used.*

Table 3 Odds ratios and 95% CIs for curative treatment in men with diabetes and additional comorbidities compared with those with type 2 diabetes only.

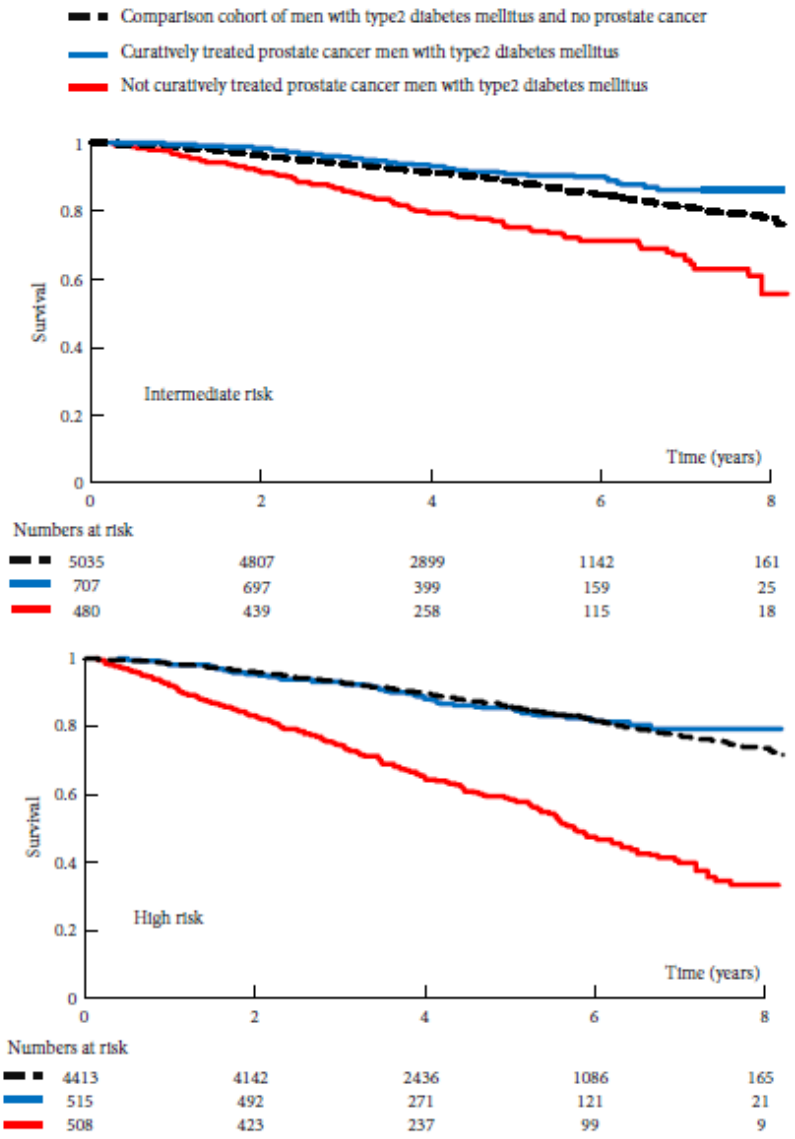
	T2DM and hypertension *		T2DM and high cholesterol *		T2DM and CVD‡	
Model	**OR**	**CI**	**OR**	**CI**	**OR**	**CI**
Crude	0.54	0.49–0.60	0.58	0.52–0.65	0.48	0.40–0.57
Age	0.73	0.65–0.81	0.73	0.65–0.83	0.66	0.54–0.81
CCI†	0.79	0.70–0.88	0.80	0.71–0.91	0.79	0.64–0.97
T stage	0.80	0.71–0.90	0.81	0.71–0.93	0.80	0.65–0.98
Gleason	0.75	0.67–0.85	0.77	0.67–0.88	0.75	0.60–0.92
PSA‡	0.76	0.68–0.85	0.77	0.67–0.88	0.75	0.61–0.93
% positive cores	0.75	0.66–0.84	0.76	0.66–0.87	0.72	0.58–0.89
Mode of detection	0.76	0.68–0.86	0.77	0.68–0.89	0.74	0.59–0.92
Education	0.77	0.68–0.87	0.79	0.68–0.90	0.75	0.60–0.93
Marital status	0.78	0.69–0.88	0.79	0.69–0.90	0.75	0.60–0.93

*CCI, Charlson comorbidity index; CVD, cardiovascular disease; OR, odds ratio; T2DM, type 2 diabetes mellitus. The ORs are taken from a multivariate model including all covariates listed. *Cardiovascular disease, hypertension and high cholesterol were defined by filled prescriptions drugs for these conditions in the Prescribed Drug Register. †Calculated excluding diabetes. ‡For PSA linear splines with knots at 3, 10 and 20 were used.*

selection of the healthiest men and allocation to curative treatment among men with T2DM and PCa was indicated by the fact that these men had a better overall survival than corresponding PCa-free men with T2DM (Fig. 1). The selection of healthy men for curative treatment is also highlighted by the lower 90-day mortality after RP compared with the background population in a previous Swedish study [25]. Williams and Huo [26] have also demonstrated this selection bias, showing a survival advantage in men receiving both RP and RT vs a PCa-free comparison cohort. This selection was also reflected in the present study in PCa-specific mortality (Fig. 2), which remained low regardless of PCa treatment for intermediate-risk disease. The higher proportion of death from other causes in men not curatively treated confirms that these men have high comorbidity with ensuing increased risk of death from competing causes. In men with conservatively treated high-risk PCa, however, 22% died from PCa within 8 years of diagnosis, suggesting that a larger proportion of these men should have received curative treatment. In the present study, we also show that men with T2DM were more likely to receive primary androgen deprivation therapy than those without T2DM (25% vs 15% [Table 1]). Given the metabolic and cardiovascular side effects of androgen deprivation therapy, this is another reason to ensure that men with PCa and T2DM are not undertreated with respect to curative treatment.

The strengths of the present study include its large size, the population-based design and the comparison cohort of PCa-free men with T2DM. Furthermore, we had access to data from a number of nationwide population-based high-quality registers, including the Prescribed Drug Register, the Inpatient Register, the Cause of Death Register and the National Diabetes Register. Limitations include the fact that we only had 8 years of follow-up data instead of the conventional 10-year survival curves or estimated life expectancies. A further limitation is that, by using drug

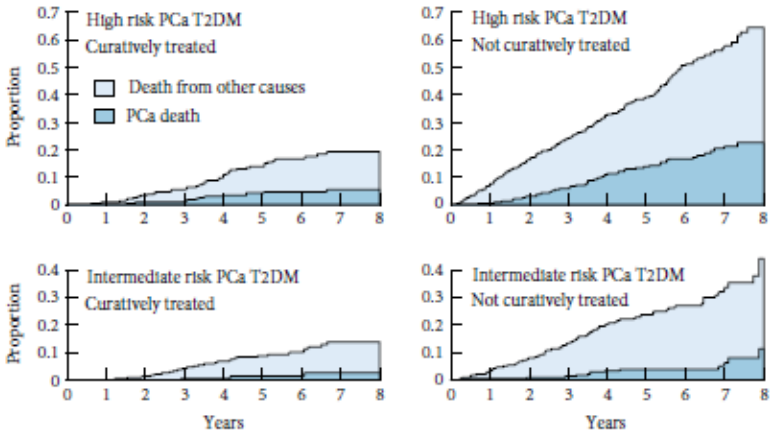
Fig. 1 Overall survival for men with type 2 diabetes mellitus according to prostate cancer risk category and prostate cancer treatment.



prescriptions as a proxy for T2DM, we would have missed all T2DM cases treated by diet alone; however, diet-controlled T2DM is unlikely to have influenced PCa treatment decisions. We show that, in fact, it was only those treated with insulin who were less likely to receive curative treatment. As discussed above, we acknowledge that a selection bias of the healthiest men to receive curative treatment among men with T2DM and PCa exists. This was indicated by the fact that these men had better overall survival times than corresponding PCa-free men with T2DM. Confounding by indication may also have influenced selection for curative treatment, i.e. those with the most favourable prognosis may have preferentially been chosen for curative treatment. By adjusting for tumour characteristics we have accounted for this as much as possible; however, as with all observational data, there may be some residual confounding.

In conclusion, men with T2DM were less likely to receive curative treatment for localized PCa. Men with T2DM and high-risk PCa who received curative treatment had

Fig. 2 Cumulative incidence of prostate cancer (PCa)-specific death and death from other causes according to PCa risk category and treatment. T2DM, type 2 diabetes mellitus.



substantially higher survival rates than men with T2DM and PCa who were conservatively treated. Some of the survival differences represent a selection bias of the healthiest patients to receive curative treatment, but of the men with conservatively treated high-risk PCa, 22% died specifically from PCa, suggesting that a larger proportion of these men should have received curative treatment. Clinicians should interpret these data carefully and ensure that individual patients with T2DM and PCa are not under- nor overtreated.

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Conflict of Interest

The results and views expressed in the study represent those of the authors and not necessarily those of the Swedish Medical Products Agency, at which one of the authors (Björn Zethelius) is employed. Björn Zethelius has not received any grants or any financial support from any sponsor for the present work. No authors declare any conflicts of interest.

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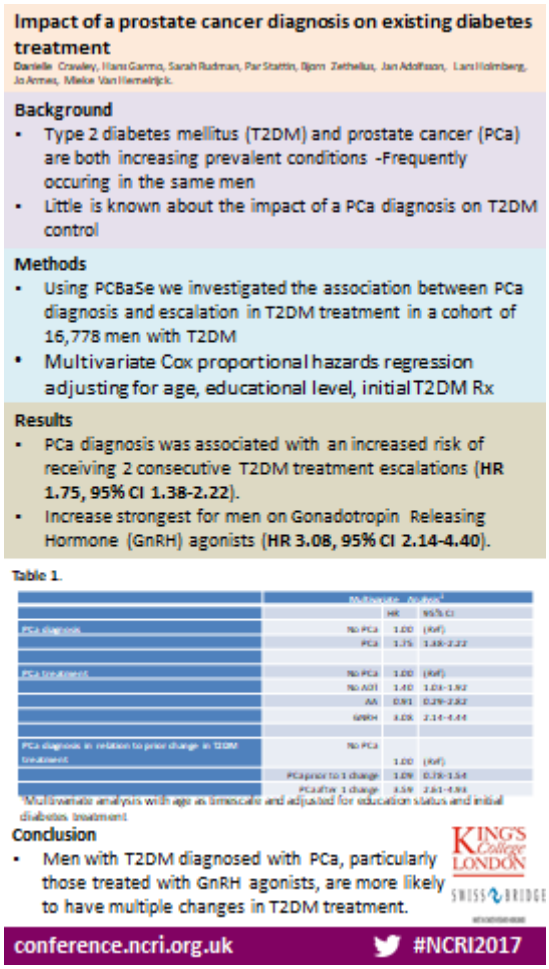
Abbreviations: PCa, prostate cancer; T2D, Type 2 diabetes mellitus; PCBaSe, Prostate Cancer database Sweden; CCI, Charlson comorbidity index; NPCR, National Prostate Cancer Register of Sweden; RP, radical prostatectomy; RT, radiotherapy; ATC, Anatomical Therapeutic Chemical; MICE, multivariate imputation using chained equations; CVD, cardiovascular disease; OR, odds ratio.

Appendix 2



Impact of a prostate cancer diagnosis on existing diabetes treatment

Danielle Crawley, Hans Garmo, Sarah Rudman, Par Stattin, Bjorn Zethelius, Jan Adolfsson, Lars Holmberg, Jo Armes, Mieke Van Hemelrijck.

Background

- Type 2 diabetes mellitus (T2DM) and prostate cancer (PCa) are both increasing prevalent conditions -Frequently occuring in the same men
- Little is known about the impact of a PCa diagnosis on T2DM control

Methods

- Using PCBaSe we investigated the association between PCa diagnosis and escalation in T2DM treatment in a cohort of 16,778 men with T2DM
- Multivariate Cox proportional hazards regression adjusting for age, educational level, initial T2DM Rx

Results

- PCa diagnosis was associated with an increased risk of receiving 2 consecutive T2DM treatment escalations (**HR 1.75, 95% CI 1.38-2.22**).
- Increase strongest for men on Gonadotropin Releasing Hormone (GnRH) agonists (**HR 3.08, 95% CI 2.14-4.40**).

Table 1.

	Multivariate Analysis[1]	
	HR	95% CI
PCa diagnosis		
No PCa	1.00	(Ref)
PCa	1.75	1.38-2.22
PCa treatment		
No PCa	1.00	(Ref)
No AGI	1.40	1.01-1.92
AA	0.91	0.29-2.82
GNRH	3.08	2.14-4.44
PCa diagnosis in relation to prior change in T2DM treatment		
No PCa	1.00	(Ref)
PCa prior to 1 change	1.09	0.78-1.54
PCa after 1 change	3.59	2.61-4.93

[1]Multivariate analysis with age as timescale and adjusted for education status and initial diabetes treatment

Conclusion

- Men with T2DM diagnosed with PCa, particularly those treated with GnRH agonists, are more likely to have multiple changes in T2DM treatment.

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Appendix 3

Association between duration and type of Androgen Deprivation Therapy and risk of diabetes in men with prostate cancer

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Introduction:

- Androgen Deprivation Therapy (ADT) is the recommended first line treatment in men with disseminated prostate cancer (PCa)
- Due to the prolonged disease trajectory of PCa, men can remain on ADT for many years making any long term effects associated with treatment significant
- Adverse effects of ADT include hot flushes, impotence, fatigue, increased risk of cardiovascular disease and reduced bone mineral density
- Several North American cohorts have also shown that ADT increases the risk of type 2 diabetes (T2DM)
- This led to the Food and Drug Administration (FDA) adding a risk label on gonadotropin-releasing hormone (GnRH) agonists for increased risk of T2DM
- However, the effect of the different types of ADT and their duration is not known

Study population/Methods:

- Prostate Cancer database Sweden 3.0 (**PCBaSe**) is based on the National Prostate Cancer Register (NPCR) which became nationwide in 1998 and covers 98% PCa cases
- It is linked to a number of national health care registers and demographic databases including the National Prescribed Drug Register from 2006
- We investigated risk of T2DM in a cohort of **34,031 men with PCa** on ADT compared to **167,205 men in an age-matched, PCa-free comparison cohort** within PCBaSe
- Multivariate Cox proportional hazard regression was used , with age as the time scale, accounting for Charlson Co-morbidity Index, education status and PCa risk category
- Using ATC codes we searched the National Prescribed Drug Register for two subsequent newly filled prescriptions for metformin, sulphonylurea or insulin and this was used as a proxy outcome for a new diagnosis of T2DM
- Incidence rates of T2DM per 1,000 person/years were also calculated for the different ADT exposure groups

Results:

	PCa Free Cohort	All men with PCa	AA	GnRH	Orchiectomy
n [%]	167,205	34,031	9,143	21,874	3,014
Mean Follow up time (SD)	4.2 (2.5)	3.5 (2.4)	3.6 (2.5)	3.5 (2.4)	3.1 (2.4)
Age					
Mean age at diagnosis (SD)	74.8 (8.5)	74.4 (8.4)	71.2 (8.0)	75.2 (8.3)	78.4 (7.3)
<65	23183 (13.9)	4908 (14.4)	2119 (23.2)	2623 (12.0)	166 (5.5)
65-74	93548 (55.1)	11806 (54.7)	3895 (42.6)	7247 (33.1)	666 (22.1)
75-84	70809 (42.3)	14136 (41.5)	2829 (30.9)	9655 (44.1)	1652 (54.8)
85+	17865 (10.7)	3181 (9.3)	301 (3.3)	2349 (10.7)	530 (17.6)
Age at start of ADT					
<65	- -	3592 (10.6)	1189 (13.0)	2254 (10.3)	149 (4.9)
65-74	- -	10849 (51.9)	3641 (39.8)	6596 (30.2)	612 (20.3)
75-84	- -	15495 (45.5)	3766 (41.2)	10059 (46.0)	1668 (55.3)
85+	- -	4097 (12.0)	547 (6.0)	2965 (13.6)	585 (19.4)
Entry into PCBaSe cohort					
1997-2001	17889 (10.7)	5389 (15.8)	1145 (12.5)	3687 (16.9)	557 (18.5)
2002-2005	49575 (29.5)	11281 (33.1)	2738 (29.9)	7446 (34.0)	1097 (36.4)
2006-2009	64085 (38.3)	11567 (34.0)	3438 (37.6)	7161 (32.7)	968 (32.1)
2010-2012	35856 (21.4)	5794 (17.0)	1822 (19.9)	3580 (16.4)	392 (13.0)
CCI					
0	110713 (66.2)	22528 (66.8)	6271 (68.6)	14143 (64.7)	1914 (65.5)
1	29651 (17.7)	6247 (18.4)	1587 (17.4)	4048 (18.5)	612 (20.3)
2	15948 (9.5)	3309 (9.7)	793 (8.7)	2215 (10.1)	301 (10.0)
3+	10893 (6.5)	2147 (6.3)	492 (5.4)	1468 (6.7)	187 (6.2)
Education Status					
Low	78732 (47.1)	16239 (47.7)	3559 (38.9)	10898 (49.8)	1782 (59.1)
Middle	56051 (33.5)	11579 (34.0)	3422 (37.4)	7252 (33.2)	905 (30.0)
High	29171 (17.4)	5771 (17.0)	2091 (22.9)	3403 (15.6)	277 (9.2)
Missing	3251 (1.9)	442 (1.3)	71 (0.8)	321 (1.5)	50 (1.7)
PCa risk category					
No PCa	167205 (100.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
1. Low risk	- -	2354 (6.9)	1180 (12.9)	1068 (4.9)	86 (2.9)
2. Intermediate risk	- -	6011 (17.7)	2819 (30.8)	2929 (13.4)	273 (9.1)
3. High risk	- -	11775 (34.6)	3469 (37.9)	7410 (33.9)	896 (29.7)
4. Regionally metastatic	- -	4745 (13.9)	962 (10.5)	3354 (15.3)	429 (14.2)
5. Distant metastases	- -	8850 (26.0)	591 (6.5)	6956 (31.8)	1303 (43.2)
6. Missing data	- -	306 (0.9)	122 (1.3)	157 (0.7)	27 (0.9)
Primary Treatment					
No PCa	167205 (100.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
ADT	- -	24815 (72.9)	4113 (45.0)	17972 (82.2)	2730 (90.6)
Curative treatment	- -	4592 (12.8)	2687 (51.6)	1402 (6.4)	63 (2.1)
Deferred treatment	- -	4864 (14.3)	2145 (23.4)	3500 (11.4)	221 (7.3)

Table 1: Baseline characteristics of men with PCa on ADT and the matched comparison cohort of PCa-free men in PCBaSe 3.0

- Table 1 shows that there was a 5 fold higher occurrence of metastatic disease at diagnosis in the GnRH treated group compared to the AA group (32 vs. 6 %)
- Conversely 5 times as many men in the AA group had undergone primary curative treatment and subsequently received ADT as in the GnRH group

	[A] Insulin/su/met	[A] Insulin	[A] Su/met
No ADT	10.44	1.47	8.97
AA	8.05	1.06	6.99
GnRH/Orch	13.01	2.98	10.04

Table 4: Incidence of T2DM per 1,000/person years in PCa-free men and men with PCa on Anti-androgens (AA) or Chemically/ Medically Castrated (GnRH/ Orch)

- The incidence of T2DM for those without ADT was 10/1,000 person-years, for men either on GnRH agonists or surgically castrated it was 13 /1,000 person-years and for men on AA it was 8/1,000 person-years

AA years of exposure	Insulin/su/met: No Events	Crude HR	95% CI	Adjusted HR*	95% CI
No ADT	7932	1	Ref.	1	Ref.
AA 0-2	126	0.73	(0.61 - 0.88)	0.73	(0.61 - 0.87)
AA 2-4	71	0.7	(0.54 - 0.89)	0.71	(0.56 - 0.91)
AA >4	61	0.76	(0.58 - 0.99)	0.8	(0.61 - 1.05)

Table 2: Event counts and Hazard ratios for receiving Insulin, sulphonylurea or metformin in men on Anti Androgens (AA) compared to a comparison cohort of PCa- free men
*Adjusted for Charlson Co-morbidity, education status and PCa Stage

GnRH / Orchiectomy years of exposure	Insulin/su/met: No Events	Crude HR	95% CI	Adjusted HR*	95% CI
No ADT	7932	1	Ref.	1	Ref.
0.5 -1	162	1.54	(1.31 - 1.80)	1.51	(1.28 - 1.79)
1-1.5	156	1.62	(1.38 - 1.91)	1.61	(1.36 - 1.91)
1.5-2	132	1.47	(1.23 - 1.76)	1.48	(1.23 - 1.78)
2-2.5	132	1.67	(1.40 - 2.00)	1.68	(1.40 - 2.02)
2.5-3	104	1.41	(1.15 - 1.73)	1.42	(1.16 - 1.74)
3-4	145	1.15	(0.97 - 1.37)	1.17	(0.98 - 1.40)
4-5	127	1.14	(0.94 - 1.39)	1.19	(0.97 - 1.45)
5-6	91	1.06	(0.84 - 1.33)	1.11	(0.88 - 1.40)
6-7	67	0.95	(0.72 - 1.24)	1.01	(0.77 - 1.33)
7-10	101	0.87	(0.71 - 1.08)	0.96	(0.77 - 1.19)
>10	30	0.6	(0.40 - 0.92)	0.69	(0.45 - 1.05)

Table 3: Event counts and Hazard ratios for receiving Insulin, sulphonylurea or metformin in men chemically or medically castrated (GnRH /Orch) compared to a comparison cohort of PCa- free men
*Adjusted for Charlson Co-morbidity, education status and PCa stage

- No increased risk of T2DM was seen in men on Anti-Androgens (AA) over any time of exposure studied
- Conversely those either medically (GnRH agonists) or surgically (orchiectomy) castrated had an increased risk of T2DM
- This risk was highest in the first 3 years of exposure (HR at 2-2.5 years of 1.68 (95% CI 1.40-2.02))
- The risk reduced over longer exposure times (HR at 7-10 years of 0.96 (95% CI 0.77-1.19))
- This is shown graphically in Figure 1 below

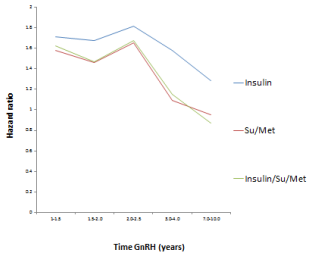

Figure 1: Graphical representation of risk of T2DM by time on GnRH agonists, T2DM was defined as A) Insulin, B) Sulphonylurea or metformin, C) Insulin, sulphonylurea or metformin.

Conclusions

- Duration of exposure to GnRH agonists has a significant impact on risk of developing T2DM in men with PCa
- Peak risk is observed after 2-3 years of treatment
- No increased risk of T2DM is seen with AA
- Strengths of this study are its large size, coverage of PCa cases in PCBaSe, availability of a comparison cohort and the long duration of exposure to ADT
- This is the first time the risk of T2DM has been demonstrated in a European cohort
- These findings may help focus efforts to address the risk of T2DM during GNRH treatment

The Royal Society of Medicine

Oncology Section

This is to certify that

Dr Danielle Crawley

Was shortlisted and presented at the

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Wednesday 15 June 2016

Susie Stanway

Dr Susannah Stanway
President
Oncology Section
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Association between duration and type of androgen deprivation therapy and risk of diabetes in men with prostate cancer

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Cancer Epidemiology

Androgen deprivation therapy (ADT) for prostate cancer (PCa) increases risk of type 2 diabetes (T2DM); however the association between types and duration of ADT has not been fully elucidated. We examined how type and duration of ADT affects risk of T2DM. Using data from Prostate Cancer database Sweden (PCBaSe) we investigated risk of T2DM in a cohort of 34,031 men with PCa on ADT; *i.e.*, anti-androgens (AA), orchiectomy, or gonadotropin-releasing hormone (GnRH) agonists compared to an age-matched, PCa-free comparison cohort ($n = 167,205$) using multivariate Cox proportional hazard regression. T2DM was defined as a newly filled prescription for metformin, sulphonylurea, or insulin in the Prescribed Drug Register. A total of 21,874 men with PCa received GnRH agonists, 9,143 AA and 3,014 underwent orchiectomy. Risk of T2DM was increased in men in the GnRH agonists/orchiectomy group during the first 3 years of ADT [*i.e.*, 1 – 1.5 years HR: 1.61 (95%CI: 1.36 – 1.91)], compared to PCa-free men. The risk decreased thereafter (*e.g.*, 3 – 4 years HR: 1.17 (95% CI: 0.98 – 1.40)). Conversely, no increased risk was seen in men on AA (HR: 0.74 (95%CI: 0.65 – 0.84). The incidence of T2DM per 1,000 person-years was 10 for PCa-free men, 8 for men on AA, and 13 for men on GnRH agonists/orchiectomy. Duration of ADT has a significant impact on risk of T2DM. With the peak after three years of treatment, our data indicates that men on ADT, even for a limited period of time, such as adjuvant to radiotherapy, are at increased risk of T2DM.

Key words: prostate cancer, type two diabetes, androgen deprivation therapy
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Androgen Deprivation Therapy (ADT) is the recommended first line treatment in all men with disseminated prostate cancer (PCa) and is also used in conjunction with radiotherapy in locally advanced disease as both neoadjuvant and adjuvant therapy.[1] When men progress to castrate resistance, it is recommended that treatment with ADT continues, alongside the addition of further therapies. Given the prolonged disease trajectory of PCa, men can remain on ADT for many years,[2] making any long-term effects associated with treatment significant.

Common adverse effects of ADT include fatigue, hot flushes and impotence.[3] ADT also increases the risk of cardiovascular disease,[4,5] reduces bone mineral density,[6] increases risk of fractures and of type 2 diabetes (T2DM), as demonstrated by several North American cohorts.[7–10] This led the Food and Drug Administration (FDA) in 2010 to add a risk label on gonadotropin-releasing hormone (GnRH) agonists for increased risk of T2DM and certain cardiovascular diseases (heart attack, sudden cardiac death, and stroke).[11]

ADT increases the prevalence of metabolic syndrome components such as decreased insulin sensitivity and increased body fat.[12] We have previously undertaken a meta-analysis to quantify the association between ADT and metabolic syndrome.[13] The risk of metabolic syndrome for men on ADT increased almost two-fold, relative risk (RR) 1.75 (95% CI 1.27-

What's new?

All treatments involve tradeoffs. For patients with prostate cancer, treatment with androgen deprivation therapy (ADT) can lead to an increased risk of type II diabetes. These authors set out to analyze how the duration of treatment, and the type of ADT, affect diabetes risk. They collected data on patients receiving three types of ADT: anti-androgens, gonadotropin releasing hormone agonists, and orchiectomy, and compared them with age-matched, cancer-free controls. The risk of diabetes peaked after 3 years of treatment with GnRH agonists or orchiectomy. By contrast, patients receiving anti-androgens showed no increase in diabetes risk relative to cancer-free controls.

2.41), as compared to men not on ADT. For T2DM this relative risk was 1.36 (95% CI 1.17-1.58). Here, we investigate the risk of T2DM in men on ADT taking into account the impact of different types and durations of ADT (GnRH agonists, anti-androgens (AA), and orchiectomy) on risk of T2DM.

Methods

Study population and data collection

PCBaSe Sweden 3.0 is based on the National Prostate Cancer Register (NPCR) of Sweden, which became nationwide in 1998 and covers 98% of all newly diagnosed cases of PCa, as compared to the Swedish Cancer Register.[14,15] NPCR includes information on date of diagnosis, age at diagnosis, tumour stage and differentiation, serum levels of prostate specific antigen (PSA) at time of diagnosis, and primary treatment within 6 months after date of diagnosis. Risk categories were determined according to a modified version of the National Comprehensive Cancer Network Guideline[16] as follows: Low risk: T1-2, Gleason score of 2–6 and PSA< 10 ng/ml; intermediate risk: T1-2, Gleason score 7 and/or PSA 10–20 ng/ml; high risk: T3and/or Gleason score 8–10 and/or PSA 20—50 ng/ml; regionally metastatic/locally advanced:T4 and/or N1 and/or PSA 50–100 ng/ml in the absence of distant metastases (M0 or MX); distant metastases: M1 and/or PSA > 100 ng/ml. Using the Swedish 10-digit personal identity number, five PCa-free men from the general population in Sweden were randomly selected within sets of men who matched the index case on birth year and county of residence and included in the PCBaSe comparison cohort.[14] Cases and the comparison cohort in PCBaSe were subsequently linked to a series of national health care registers and demographic databases, in order to obtain data on comorbidity, socioeconomic status, and cause of death. Information on filled prescriptions of anti-androgens (AA), gonadotropin-releasing hormone (GnRH) agonists, metformin, sulphonylurea and insulin was obtained from The National Prescribed Drug Register using ATC codes (insulin- ANA, metformin- A10BA/BD sulphonylurea- A10BB GnRH –L02AE AA- L02BB).[17] The Research Ethics Board at Umeå University approved this study.

For this analysis we selected both men who received primary and secondary ADT, *i.e.*, as a second line treatment strategy initiated after primary treatment at the time of disease progression. Primary treatment was recorded in NPCR as well as the Prescribed Drug Register, whereas secondary ADT was retrieved from the Prescribed Drug Register only.[14] Co-morbidities were measured by the Charlson Comorbidity Index (CCI), which assigns weights to a number of medical conditions, including diabetes and hypertension based on discharge diagnoses in the Patient Register.[18] Each condition was assigned a score of 1, 2, 3, or 6 and the final CCI is given as the sum of these scores. Individuals were grouped into CCI categories for final scores of 0, 1, 2, or 3+. Information on age at diagnosis, primary treatment, education status, and prostate cancer risk category were also used.

Analysis

We conducted an analysis whereby PCa men on ADT and PCa-free men were followed to identify occurrence of T2DM. The latter was defined by two filled prescriptions for insulin, metformin or sulphonylurea with a maximum time between the two prescriptions of 180 days. The date of the first filled prescription was used as the date of the event. Hazard ratios (HRs) for T2DM were calculated for men with PCa versus the comparison cohort with left truncation using a Cox proportional hazards model with age as a timescale accounting for CCI, PCa risk category and education status. Left truncation was applied because the Prescribed Drug Register started on July 1st 2005. We allowed for a run-in period of six months and men with a filled prescription for anti-diabetic drugs during this period were excluded from the analysis. Hence, all men with prevalent T2DM on an anti-diabetic drug were excluded. Follow up started on 1st January 2006 and ended at date of death, date of emigration, date of T2DM prescription, or 31 December 2013, whichever came first. Men who received AA or GnRH according to NPCR and had a date of diagnosis prior to 1st January 2006 and were found to still be receiving them according to the Prescribed Drug Register during the "run in period" were considered to have been "exposed" since the date of diagnosis.[15] All other exposure to AA or GNRH was defined as time from first filled prescription. In case of cross over, patients were allowed to change groups and were from then onwards considered to be exposed to the treatment in their new group. Thereby, these persons contributed person/years in each treatment category.

The association between duration of ADT and risk of T2DM was assessed using multivariate Cox proportional hazards models with left truncation in which exposure time was divided into the following intervals: 0–6 months, 6–12

months, 12–18 months, 18–24 months, 24–30 months, 30–36 months, 36–48 months, 48–60 months, 60–72 months, 72–84 months, 84–120 months, >120 months. We also calculated incidence rates per 1,000/person years for the different exposure groups. Finally, we conducted a sensitivity analysis in which incidence rates of T2DM were compared between men with PCa 2 years prior to initiation of ADT and men 2 years post initiation of ADT. This analysis included men free of T2DM who received their first ADT after 1st of August 2008 to ensure that sufficient data was available from the National Prescribed Drug Register which only start on 1st July 2005.Those men in the sensitivity analysis who developed T2DM in the period 0–2 years prior to ADT were obviously not included in the overall analysis. All data management was performed with SAS version 9.3 (SAS Institute, Cary, NC) and all data analysis was conducted with R version 2.13.2 (R Foundation for Statistical Computing, Wien, Austria).

Results

167,205 PCa-free men and 34,031 men with PCa out of whom 21,874 (64%) received GnRH agonists, 9,143 (27%) AA and 3,014 (9%) underwent orchiectomy were included in the study (Table 1). Results for men who had undergone surgical or medical castration were analyzed together in the GnRH/Orch group.

There was a five-fold higher occurrence of metastatic disease at date of diagnosis among men in the GnRH compared to men on AA (32% *vs.* 6%). Conversely, five times as many men on AA had undergone primary curative treatment and subsequently received ADT, compared to men on GnRH (31% vs. 6%) (Table 1).

Table 2 shows the number of events and HRs for men receiving a new prescription for insulin, sulphonylurea or metformin on AA or GnRH/Orch over time compared to a PCa free cohort. Those in the GnRH/Orch group had an increased risk, up until 2.5–3 years of exposure, HR 1 − 1.5 years of ADT 1.61 (95% CI 1.36 − 1.91), 2 − 2.5 years of ADT 1.68 (95% CI:1.4 − 2.02), 2.5–3 years of ADT 1.42 (95% CI 1.16 − 1.76) which then reduced, 3–4 years of ADT 1.17 (95% CI0.98 − 1.40) and 7–10 years ADT 0.96 (95% CI 0.77 − 1.19). In contrast, those on AA had no increased risk of T2DM during any time period compared to PCa-free men, HR during 0–2 years of ADT 0.73 (95% CI: 0.61 − 0.87), 2–4 years: 0.71 (95% CI 0.56 − 0.91) and >4 years 0.80 (95% CI 0.61 − 1.05).

In the subgroup of men treated with insulin only (Table 2) there was a persistent increase in risk observed during all time periods for men in the GnRH/Orch group, peaking at 2.5–3 years with a HR of 2.32 (95% CI: 1.67 − 3.21). In contrast, those on AA had no increased risk of T2DM during any time period compared to PCa-free men.

Table 2 reports the corresponding results for those receiving either metformin or sulphonylurea. Those in the GnRH/Orch group had a significantly elevated risk until 2 − 2.5 years of exposure (HR: 1.65 (95%CI: 1.35 − 2.02) before a reduction in later time periods and became nonstatistically significant. Similarly to insulin, no increased risk of T2DM was seen in those on AA at any time period. The time-dependent results of Table 2 are also illustrated in Figure 1.

The incidence of T2DM for those without ADT was 10/1,000 person-years, for men on GnRH agonists/orchiectomy 13/1,000 person-years and 8/1,000 person-years for men on AA (Table 3). The results of the sensitivity analysis comparing the incidence of T2DM in men with PCa 2 years prior and after initiation of ADT are presented in Table 4. A similar increase in risk for T2DM was observed. In men treated with AA the incidence of T2DM (receiving insulin) was 1.5 *vs.* 1.7/1,000 person-years 2 years before and after ADT. In those treated with GnRH/Orch, the incidence of T2DM (receiving insulin) was 2.2 *vs.* 5.0/1,000 person-years, respectively, and for T2DM (receiving metformin/sulfonylurea) 11.1 vs. 11.3/1,000 person-years.

Discussion

In accordance with previous studies, this large nation-wide population-based cohort study showed that men on ADT had an increased risk of T2DM as defined by filled prescriptions for an anti-diabetic drug In addition, the highest risk of T2DM was reached at 3 years after the start of GnRH/Orch. In contrast, men on monotherapy anti-androgens had no such increase.

In the first study on risk of T2DM for men on GnRH agonists, Keating *et al.* showed an increased risk in men aged >66 with loco-regional PCa (HR for GnRH agonists versus no ADT: 1.44, 95% CI: 1.34-1.55).[7] However, this study had a relatively short duration of exposure, *i.e.*, 1–4, 5–12, 13–24, >25 months. The same authors obtained similar results in a further study including men of all ages with loco-regional PCa.[10] They analyzed combined androgen blockade and AA separately and did not show an increased risk of T2DM. The effect of duration of treatment on risk of T2DM was not examined. A similar study was conducted by Alibhai *et al.* in a Canadian cohort of men aged ≥66 years who received at least 6 months of ADT.[8] They also reported an increased risk of T2DM (HR: 1.16, 95% CI: 1.11 − 1.21), but did not examine GnRH and AA separately and combined all forms of ADT as a single exposure. There was a trend toward increased risk of diabetes with longer exposure to ADT (HR for ADT *vs.* no ADT: 1.09, 95% CI: 0.9 − 1.08 >24 months of exposure compared with HR: 0.99, 95% CI 0.90 − 1.08 at 6–24 months).

The longest duration of follow up to date was 25 months.[7] No studies have looked at different types of ADT and the effect of duration combined. AA use in North America is substantially lower than in Europe, so there are little data from these cohorts on AA. We examined the risk of T2DM with up to ten years of exposure, which is to our knowledge the longest exposure studied to date. The highest risk associated with GnRH agonists occurred relatively early and started to decline after 3 years of treatment. For AA we did not observe an increased risk.

The observed temporal changes in risk fit with the physiological and metabolic changes previously described for GnRH agonist treatment.[19] These changes include increased fat

Table 1. Baseline characteristics of men with PCa on ADT and the matched comparison cohort of PCa-free men in Prostate Cancer Data Base 3.0

	PCa Free Cohort		All men with PCa		AA		GnRH		Orchiectomy	
n (%)	167,205		34,031		9,143		21,874		3,014	
Mean Follow up time (SD)										
	4.2	(2.5)	3.5	(2.4)	3.6	(2.3)	3.5	(2.4)	3.1	(2.4)
Age										
Mean age at diagnosis (SD)	74.8	(8.5)	74.4	(8.4)	71.2	(8.0)	75.2	(8.3)	78.4	(7.3)
<65	23183	(13.9)	4908	(14.4)	2119	(23.2)	2623	(12.0)	166	(5.5)
65-74	55348	(33.1)	11806	(34.7)	3893	(42.6)	7247	(33.1)	666	(22.1)
75-84	70809	(42.3)	14136	(41.5)	2829	(30.9)	9655	(44.1)	1652	(54.8)
85+	17865	(10.7)	3181	(9.3)	302	(3.3)	2349	(10.7)	530	(17.6)
Age at start of ADT										
<65	-	-	3592	(10.6)	1189	(13.0)	2254	(10.3)	149	(4.9)
65-74	-	-	10849	(31.9)	3641	(39.8)	6596	(30.2)	612	(20.3)
75-84	-	-	15493	(45.5)	3766	(41.2)	10059	(46.0)	1668	(55.3)
85+	-	-	4097	(12.0)	547	(6.0)	2965	(13.6)	585	(19.4)
Entry into PCBaSe cohort/Year of PCa diagnosis										
1997-2001	17889	(10.7)	5389	(15.8)	1145	(12.5)	3687	(16.9)	557	(18.5)
2002-2005	49375	(29.5)	11281	(33.1)	2738	(29.9)	7446	(34.0)	1097	(36.4)
2006-2009	64085	(38.3)	11567	(34.0)	3438	(37.6)	7161	(32.7)	968	(32.1)
2010-2012	35856	(21.4)	5794	(17.0)	1822	(19.9)	3580	(16.4)	392	(13.0)
CCI										
0	110713	(66.2)	22328	(65.6)	6271	(68.6)	14143	(64.7)	1914	(63.5)
1	29651	(17.7)	6247	(18.4)	1587	(17.4)	4048	(18.5)	612	(20.3)
2	15948	(9.5)	3309	(9.7)	793	(8.7)	2215	(10.1)	301	(10.0)
3+	10893	(6.5)	2147	(6.3)	492	(5.4)	1468	(6.7)	187	(6.2)
Education Status										
Low	78732	(47.1)	16239	(47.7)	3559	(38.9)	10898	(49.8)	1782	(59.1)
Middle	56051	(33.5)	11579	(34.0)	3422	(37.4)	7252	(33.2)	905	(30.0)
High	29171	(17.4)	5771	(17.0)	2091	(22.9)	3403	(15.6)	277	(9.2)
Missing	3251	(1.9)	442	(1.3)	71	(0.8)	321	(1.5)	50	(1.7)
PCa risk category										
No PCa	167205	(100.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
1. Low risk	-	-	2334	(6.9)	1180	(12.9)	1068	(4.9)	86	(2.9)
2. Intermediate risk	-	-	6021	(17.7)	2819	(30.8)	2929	(13.4)	273	(9.1)
3. High risk	-	-	11775	(34.6)	3469	(37.9)	7410	(33.9)	896	(29.7)
4. Regionally metastatic	-	-	4745	(13.9)	962	(10.5)	3354	(15.3)	429	(14.2)
5. Distant metastases	-	-	8850	(26.0)	591	(6.5)	6956	(31.8)	1303	(43.2)
6. Missing data	-	-	306	(0.9)	122	(1.3)	157	(0.7)	27	(0.9)
Primary Treatment										
No PCa	167205	(100.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
ADT	-	-	24815	(72.9)	4113	(45.0)	17972	(82.2)	2730	(90.6)
Curative treatment	-	-	4352	(12.8)	2887	(31.6)	1402	(6.4)	63	(2.1)
Deferred treatment	-	-	4864	(14.3)	2143	(23.4)	2500	(11.4)	221	(7.3)

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Table 2. Hazard ratios for insulin, sulphonylurea or metformin, insulin, or sulphonlyurea or Metfomnin, in men on ADT compared to a comparison cohort of PCa-free men

	Insulin/su/met					Insulin					Su/met				
ADT years of exposure	No Events	Crude HR	95% CI	Adjusted HR*	95% CI	No Events	Crude HR	95% CI	Adjusted HR*	95% CI	No Events	Crude HR	95%CI	Adjusted HR*	95%CI
No ADT	7932	1	Ref.	1	Ref.	1688	1	Ref.	1	Ref.	6320	1	Ref.	1	Ref.
AA 0-2	126	0.73	(0.61 – 0.88)	0.73	(0.61 – 0.87)	27	0.78	(0.53 – 1.14)	0.76	(0.52 – 1.11)	100	0.67	(0.55 – 0.82)	0.68	(0.56 – 0.83)
AA 2-4	71	0.7	(0.54 – 0.89)	0.71	(0.56 – 0.91)	16	0.82	(0.50 – 1.34)	0.83	(0.51 – 1.36)	55	0.69	(0.53 – 0.90)	0.71	(0.54 – 0.92)
AA >4	61	0.76	(0.58 – 0.99)	0.8	(0.61 – 1.05)	9	0.54	(0.28 – 1.05)	0.59	(0.30 – 1.13)	52	0.84	(0.64 – 1.10)	0.88	(0.67 – 1.16)
GnRH 0 –0.5	157	1.44	(1.23 – 1.70)	1.41	(1.20 – 1.67)	36	1.52	(1.09 – 2.12)	1.31	(0.93 – 1.85)	124	1.35	(1.13 – 1.61)	1.38	(1.15 – 1.66)
GnRH 0.5 –1	162	1.54	(1.31 – 1.80)	1.51	(1.28 – 1.79)	41	1.82	(1.33 – 2.47)	1.59	(1.15 – 2.19)	126	1.45	(1.21 – 1.73)	1.49	(1.24 – 1.80)
GnRH 1-1.5	156	1.62	(1.38 – 1.91)	1.61	(1.36 – 1.91)	40	1.91	(1.40 – 2.62)	1.71	(1.24 – 2.37)	120	1.52	(1.27 – 1.82)	1.58	(1.31 – 1.90)
GNRH 1.5-2	132	1.47	(1.23 – 1.76)	1.48	(1.23 – 1.78)	35	1.84	(1.32 – 2.57)	1.67	(1.18 – 2.36)	100	1.4	(1.15 – 1.71)	1.46	(1.19 – 1.79)
GnRH 2-2.5	132	1.67	(1.40 – 2.00)	1.68	(1.40 – 2.02)	34	1.96	(1.40 – 2.76)	1.81	(1.27 – 2.56)	102	1.59	(1.30 – 1.93)	1.65	(1.35 – 2.02)
GnRH 2.5-3	104	1.41	(1.15 – 1.73)	1.42	(1.16 – 1.76)	39	2.49	(1.81 – 3.42)	2.32	(1.67 – 3.21)	67	1.17	(0.92 – 1.49)	1.23	(0.96 – 1.57)
GnRH 3-4	143	1.15	(0.97 – 1.37)	1.17	(0.98 – 1.40)	45	1.66	(1.23 – 2.23)	1.58	(1.16 – 2.14)	100	1.03	(0.85 – 1.26)	1.09	(0.89 – 1.33)
GnRH 4-5	127	1.14	(0.94 – 1.39)	1.19	(0.97 – 1.45)	50	2.27	(1.71 – 3.01)	2.22	(1.65 – 2.97)	78	1.02	(0.82 – 1.28)	1.09	(0.86 – 1.36)
GnRH 5-6	91	1.06	(0.84 – 1.33)	1.11	(0.88 – 1.40)	36	2	(1.44 – 2.79)	2.01	(1.43 – 2.82)	56	0.93	(0.71 – 1.20)	1	(0.76 – 1.30)
GnRH 6-7	67	0.95	(0.72 – 1.24)	1.01	(0.77 – 1.33)	27	1.88	(1.28 – 2.74)	1.91	(1.30 – 2.82)	42	0.88	(0.65 – 1.20)	0.96	(0.71 – 1.31)
GnRH 7-10	101	0.87	(0.71 – 1.08)	0.96	(0.77 – 1.19)	32	1.2	(0.85 – 1.70)	1.28	(0.89 – 1.83)	71	0.85	(0.67 – 1.07)	0.95	(0.74 – 1.20)
GnRH >10	30	0.6	(0.40 – 0.92)	0.69	(0.45 – 1.05)	16	1.51	(0.92 – 2.48)	1.72	(1.04 – 2.84)	15	0.5	(0.30 – 0.83)	0.58	(0.35 – 0.96)

mass, reduced lean body mass and increased insulin levels, which all have been demonstrated to occur within 3 months of commencing ADT.[19–21] Lee *et al.* measured lean body mass and fat mass in 65 men with PCa on GnRH agonists over a 12 month period. Those with longer prior exposure to treatment with GnRH agonists had less fat accumulation and less loss of lean body mass over the 12 month period.[20] Similarly, GnRH agonists decrease sensitivity to insulin within 3 months of ADT start.[22] Thus, the adverse metabolic effects of GnRH agonists occur within months of initiation; the consequences of these changes (*i.e.*, developing T2DM) do not peak until 2 years later.

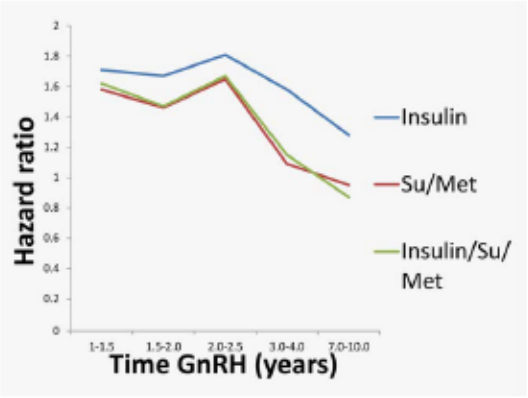

Figure 1. Graphical representation of risk of T2DM by time on GnRH agonists, T2DM was defined by anti-diabetic drug prescriptions: (a) Insulin, (b) Sulphonlurea or Metaformin, (c) Insulin, Sulphonylurea or Metformin. [Color figure can be viewed at wileyonlinelibrary.com]

Strengths of our study are its large size, population-based design of PCBaSe, and long duration of exposure to ADT. The use of an age-matched PCa-free comparison cohort allowed us to handle PCa heterogeneity. If we had used men with PCa receiving radical therapy or men on active surveillance/watchful waiting as the comparison group we would have introduced selection bias as these men have a different general health status than men with PCa on ADT. However, this approach does not allow us to tease out the disease effect. The sensitivity analysis comparing incidence rates of T2DM in men with PCa 2 years prior and after initiation of ADT aimed to assess this. The results remained consistent to what was seen when using the PCa free comparison cohort, with a higher incidence of T2DM in those receiving insulin observed after 2 years of GnRH treatment (2.2 *vs.* 5.0/1,000 person years) and not in those treated with AA.

One limitation of this study is that by using new drug prescriptions as a proxy for T2DM, we have missed all T2DM cases treated by diet alone; however, this would be similar for

Table 3. Incidence of T2DM per 1,000 person-years in PCa-free men and men with PCa on anti-androgens (AA) or GnRH agonists/orchiectomy (GnRH/Orch group). according to anti-diabetic drug prescriptions.

	No of events	Insulin/Sulphonylurea /Metformin Incidence rate	No of events	Insulin Incidence rate	No of events	Metformin /Sulphonylurea Incidence rate
No ADT	7274	10.45	1030	1.47	6244	8.97
AA	239	8.07	33	1.11	206	6.96
GNRH/Orch	1258	12.98	287	2.96	971	10.01
Prior AA	81	13.64	11	1.85	70	11.79
No Prior AA	1177	12.93	276	3.03	901	9.90

Table 4. Event number and incidence per 1,000/person years of T2DM treated with Metformin/Sulphonylurea or Insulin in men with PCa two years before and after ADT initiation.

	Metformin/Sulphonylurea				Insulin			
	2 years prior to ADT initiation		2 years after ADT initiation		2 years prior to ADT initiation		2 years after ADT initiation	
Type of ADT at initiation	No DM events	Incidence of DM	No DM events	Incidence of DM	No DM events	Incidence of DM	No DM events	Incidence of DM
All	394	10.4	301	10.1	73	1.9	113	3.8
AA	128	9.1	91	8.1	21	1.5	19	1.7
AA initial treatment	50	9.2	44	9.5	10	1.8	10	2.2
AA deferred treatment	78	9.0	47	7.1	11	1.3	9	1.4
GNRH	266	11.1	210	11.3	52	2.2	94	5.0
GNRH initial treatment	195	10.9	159	11.3	41	2.3	70	5.0
GNRH deferredtreatment	71	11.7	51	11.2	11	1.8	24	5.2

men with and without PCa. It would be interesting in future studies to be able to include this group of men. By only including two of the potential oral hypoglycaemic agents used for T2DM, metformin and sulphonylurea, we missed those with T2DM who were on alternative drugs. However, these only accounted for 1.32% of events. Another limitation of this study is that we did not have information about lifestyle factors including weight or family history of T2DM. However, all results were adjusted for CCI, which accounts for other comorbidities associated with lifestyle risk factors,[23] as well as education status—which has also been shown to be a good indicator of baseline health status.[23] Despite adjusting for several covariates, residual confounding may still be present. However, adjustment for CCI and education status reduces this possibility substantially. A further limitation is that the different risks observed between GnRH agonists and AA could potentially be explained by selection bias, rather than a real difference in the two treatments. Men treated with GnRH agonists are not only more likely to have locally advanced or distantly metastatic disease, they are also more likely to have more comorbidities than those treated with AA. Men on AA had lower PSA and T stage than those initially treated with GnRH agonists (data not shown). This reflects standard clinical practice whereby GnRH agonists are used as a primary treatment for advanced disease. Hence, men on GnRH agonists may be at higher risk of T2DM than those on AA; this however, does not diminish the clinical importance of identifying those at highest risk of T2DM during ADT.

Conclusion

Duration of GnRH agonists had a significant impact on risk of T2DM in men with PCa, with the peak risk observed after 3 years of treatment. This suggests that even men receiving adjuvant ADT, for a short time period, may be at increased risk of T2DM.

Disclaimer

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*Adjusted for CCI, PCa Stage, and Education level.

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Appendix 4

Effect of baseline metabolic aberrations in men with locally advanced/metastatic Prostate cancer treated with ADT on time to disease progression, prostate cancer specific and all cause death

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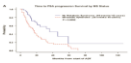
Background:

- Metabolic syndrome is defined as having 3 of the following :

- Metabolic conditions (diabetes, obesity or dyslipidaemia) have been linked with prostate cancer (PCa) aggressiveness and death.
- Flanagan et al showed a significant reduction to time to PSA progression (16 Vs. 36 months) in men with metabolic syndrome (see below).



Flanagan et al, Annals of Oncology, 2013.

- Suggesting potentially worse PCa outcomes for men with metabolic disturbances at baseline .

Study population/Methods:

- **2,617 men with locally advanced or metastatic hormone-naïve PCa** commencing long-term ADT who were randomised to the control arm (A) of the **STAMPEDE** trial (ISRCTN78818544) between 2005 and 2015 up until data was frozen on 25/10/15.
- **Baseline metabolic data routinely collected:**
  1. hypertension (SBP >140mmHg or DBP>90mmHg or confirmed history)
  2. obesity (BMI >30kg/m2)
  3. dyslipidaemia (HDL <1.9 mmol/l)
  4. impaired glycaemia (confirmed history of type 2 diabetes (T2DM)
- Those with a composite score of 3 or 4 are referred to as having **composite metabolic aberrations (CMA)**.
- Only baseline CMA data was available.
- Standard survival analysis methods were used to estimate hazard ratios and 95% confidence intervals comparing patients with and without metabolic aberrations for risk of PCa progression and death.
- PCa progression was divided into 3 outcomes: PSA, local and metastatic progression. Competing risks were not considered in this analysis.

Results:

Table 1- Baseline characteristics of men with locally advanced / metastatic PCa treated with ADT.

Population Characteristics	Total: mean (SD) n=2617	No CMA* (SD) n=1547	CMA* (SD) n=470
Age	68 (7.34)	68 (7.41)	66(6.90)
PSA (ng/L)	200.88 (914.04)	303.87 (941.97)	225.50 (773.97)
Gleason sum	8.33 (0.94)	8.32 (0.94)	8.36 (0.96)
BMI (kg/m²)	28.17 (4.61)	28.94 (4.92)	33.41 (4.07)
SBP (mmHg)	141.49 (18.21)	140.50 (18.18)	143.77 (17.71)
DBP (mmHg)	82.96 (17.68)	81.94 (15.80)	83.81 (15.29)
HDL (mmol/L)	1.50 (2.06)	1.41 (2.32)	1.23 (0.35)
Fib'ase (g/ml)	1.76 (1.67)	1.75 (1.73)	1.72 (1.30)
		Freq (%)	
Smokers	323 (12)	209 (13)	30 (5)
Non Smokers	2196 (83)	1258 (81)	438 (77)
Missing	98 (4)	90 (4)	98 (17)
T(staging):			
T0	8 (<1)	8 (<1)	0 (0)
T1	32 (1)	28 (1)	4 (0.8)
T2	214 (8)	160 (7)	54 (11)
T3	1756 (66)	1432 (66)	304 (64)
T4	474 (18)	398 (18)	76 (16)
T5	153 (5)	121 (5)	32 (6)
N0	1304 (49)	1065 (49)	239 (50)
N1	1189 (45)	984 (45)	209 (44)
N2	120 (4)	98 (4)	22 (4)
M0	1158 (42)	908 (42)	200 (42)
M1	1069 (57)	1239 (57)	270 (57)
Metabolic Disturbance:			
Hypertension	1464 (55)	1011 (47)	433 (86)
Diabetes	220 (8)	65 (3)	157 (33)
Obesity	684 (28)	277 (14)	407 (87)
Low HDL**	1840 (84)	1181 (83)	659 (99)

Table 3- Multivariate Hazard ratios for key outcome measures in men with baseline metabolic aberrations, in those with metastatic vs. non metastatic disease at baseline.

	Non-metastatic Patients at randomisation n=2309			Any metastatic at randomisation n=1328		
	N.(event)	HR*	95% CI	N.(event)	HR*	95% CI
PSA Progression						
CMA**	784	0.95	0.79-1.15	221	1.01	0.72-1.43
Hypertension	784	0.99	0.83-1.11	221	1.21	0.91-1.59
Obesity	752	0.96	0.81-1.13	209	0.99	0.74-1.34
Low HDL**	621	1.06	0.83-1.35	180	0.81	0.54-1.21
DM	784	0.92	0.70-1.21	221	1.24	0.75-2.05
Local Progression						
CMA**	146	1.65	1.07-2.54	46	0.90	0.38-2.08
Hypertension	148	1.22	0.79-1.58	46	0.84	0.45-1.41
Obesity	136	1.48	0.98-2.22	43	0.57	0.28-1.16
Low HDL**	111	1.31	0.84-2.59	36	7.31	1.62-32.92
DM	146	1.41	0.70-2.86	46	0.46	0.10-2.10
Metastatic Progression						
CMA**	428	1.26	0.96-1.64	73	1.10	0.57-2.14
Hypertension	428	1.08	0.88-1.31	73	0.95	0.58-1.56
Obesity	409	1.02	0.82-1.26	66	2.05	0.97-4.36
Low HDL**	345	1.13	0.82-1.62	61	0.95	0.44-2.06
DM	428	1.01	0.73-1.41	73	0.80	0.33-1.91

*HR >1 means increased risk ** CMA Composite metabolic aberrations ***HDL High density lipoprotein

Table 2-Hazard ratios for PSA, Local and metastatic progression for men with baseline metabolic aberrations compared to those without.

	Unadjusted			Adjusted*		
	N.(event)	HR**	95% CI	N.(event)	HR**	95% CI
PSA Progression						
CMA***	1101	0.93	0.80-1.09	1005	0.94	0.80-1.11
Hypertension	1101	0.95	0.84-1.07	1005	1.02	0.90-1.16
Obesity	1045	0.92	0.80-1.06	961	0.98	0.83-1.11
Low HDL****	840	0.99	0.82-1.21	811	0.98	0.80-1.21
Diabetes Mellitus	1099	0.94	0.73-1.18	1005	0.96	0.76-1.22
Local Progression						
CMA***	214	1.35	0.96-1.91	192	1.61	1.09-2.36
Hypertension	214	1.11	0.85-1.46	192	1.07	0.79-1.44
Obesity	200	0.96	0.71-1.31	179	1.18	0.82-1.69
Low HDL****	166	1.38	0.94-2.01	147	1.65	1.02-2.66
Diabetes Mellitus	214	0.94	0.59-1.60	192	1.11	0.59-2.09
Metastatic Progression						
CMA***	555	1.09	0.87-1.37	501	1.23	0.96-1.57
Hypertension	555	1.04	0.88-1.23	501	1.05	0.88-1.26
Obesity	519	1.02	0.85-1.21	475	1.00	0.81-1.22
Low HDL****	447	1.23	0.95-1.67	408	1.12	0.83-1.52
Diabetes Mellitus	553	0.91	0.66-1.26	501	1.06	0.74-1.51

*Adjusted for age, Gleason sum, PSA at randomisation, type of ADT and TNM stage, ** Composite metabolic aberrations ***HDL High density lipoprotein ****HR >1 means increased risk of event

SUMMARY OF RESULTS:

- Some evidence of an **increased risk of local progression** in those with CMA (HR 1.61 95% CI 1.09-2.36) *(Table2)*
- Some evidence of an increased risk of metastatic progression (HR 1.23 95% CI 0.96-1.57) *(Table 2)*
- No evidence of an increased risk of PSA progression in those with CMA (HR 0.94 95% CI 0.80-1.11) *(Table 2)*
- **Increased risk of Local progression** is only seen in the those with **metastatic disease** at randomisation (HR 1.65 95%CI 1.07-2.54) and not in those with **localised disease** at randomisation (HR 0.90 95% CI 0.38-2.08) *(Table 3)*
- No increased risk of PCa specific or all cause death (Data not shown)

Conclusions:

- We show that men who already had multiple metabolic aberrations at initiation of ADT, here referred to as CMA, had an increased risk of locally progressive disease, as compared to those without.
- A similar trend was seen with the development of metastatic disease/progression of existing metastatic disease.
- Our findings suggest that baseline metabolic aberrations may be associated with earlier treatment failure. Thus identifying a higher risk patient group in which to intensify therapy including management of metabolic risk.

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Appendix 5

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BMC Cancer

STUDY PROTOCOL Open Access

Metformin and longevity (METAL): a window of opportunity study investigating the biological effects of metformin in localised prostate cancer

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Abstract

Background: Metformin is a biguanide oral hypoglycaemic agent commonly used for the treatment of type 2 diabetes mellitus. In addition to its anti-diabetic effect, metformin has also been associated with a reduced risk of cancer incidence of a number of solid tumours, including prostate cancer (PCa). However, the underlying biological mechanisms for these observations have not been fully characterised in PCa. One hypothesis is that the indirect insulin lowering effect may have an anti-neoplastic action as elevated insulin and insulin like growth factor – 1 (IGF-1) levels play a role in PCa development and progression. In addition, metformin is a potent activator of activated protein kinase (AMPK) which in turn inhibits the mammalian target of rapamycin (mTOR) and other signal transduction mechanisms. These direct effects can lead to reduced cell proliferation. Given its wide availability and tolerable side effect profile, metformin represents an attractive potential therapeutic option for men with PCa. Hence, the need for a clinical trial investigating its biological mechanisms in PCa.

Methods: METAL is a randomised, placebo-controlled, double-blind, window of opportunity study investigating the biological mechanism of metformin in PCa. 100 patients with newly-diagnosed, localised PCa scheduled for radical prostatectomy will be randomised 1:1 to receive metformin (1 g b.d.) or placebo for four weeks (+/− 1 week) prior to prostatectomy. Tissue will be collected from both diagnostic biopsy and prostatectomy specimens. The primary endpoint is the difference in expression levels of markers of the Fatty acid synthase (FASN)/AMPK pathway pre and post treatment between the placebo and metformin arms. Secondary endpoints include the difference in expression levels of indicators of proliferation (ki67 and TUNEL) pre and post treatment between the placebo and metformin arms. METAL is currently open to recruitment at Guy's and St Thomas' Hospital and the Royal Marsden Hospital, London.

Discussion: This randomised placebo-controlled double blinded trial of metformin vs. placebo in men with localised PCa due to undergo radical prostatectomy, aims to elucidate the mechanism of action of metformin in PCa cells, which should then enable further larger stratification trials to take place.

Trial registration: EudraCT number 2014–005193-11. Registered on September 09, 2015.

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Background

The incidence of prostate cancer (PCa) has significantly increased over the past decades and will remain a significant health burden in years ahead. Patients presenting with localised disease at diagnosis are categorised into low, intermediate or high risk based on clinical stage, prostate specific antigen (PSA) level and histopathological Gleason score [1]. Current treatment options for men with intermediate and high risk disease include radical prostatectomy (open, laparoscopic or robotic) and radiotherapy with Neoadjuvant/adjuvant hormone therapy [2]. However, due to the risk of relapse in these groups, Neoadjuvant treatment has been investigated, but with disappointing results [3].

Type 2 Diabetes (T2DM) or impaired glucose tolerance are included in the cluster of disorders which comprise the metabolic syndrome (MetS) [4]. During the last decade, studies have investigated whether MetS is involved in the aetiology of PCa [5–7] [8, 9]. A meta-analysis to quantify the risk of PCa related to MetS found a pooled relative risk of 1.54 (95% CI:1.23–1.94) [4]. Recent studies have also suggested that the presence of MetS or some of its features is associated with higher grade disease in men with PCa and can lead to more rapid progression to castrate resistant PCa [10, 11].

Metformin (1,1-dimethylbiguanide hydrochloride) is a biguanide class of oral hypoglycaemic agent and commonly used for the treatment of T2DM. Metformin inhibits gluconeogenesis and reduces circulating levels of insulin [12]. It is also thought to play a role in lowering triglycerides and LDL cholesterol levels [13]. The usual dose is 2 g daily in divided doses and mild gastrointestinal discomfort with diarrhoea is the most common side effect (>10%). Other common side effects include: nausea, vomiting and abdominal pain. However, if dose escalation is perfomed carefully most patients are able to receive maximum drug dosing. Lactic acidosis is a very rare, but a serious adverse event [14]. To limit the risk of lactic acidosis, patients with risk factors for its development will be excluded from the study (renal impairment, hypoxia, congestive heart failure).

In addition to the anti-diabetic effect, metformin has also been associated with a reduced risk of various cancers, including PCa incidence and mortality in epidemiological studies [15–17]. However, the underlying biological mechanisms for these observations have yet to be fully characterised [18]. One hypothesis is that indirect insulin lowering effect may have an anti-neoplastic effect as elevated insulin and insulin like growth factor – 1 (IGF-1) levels play a role in prostate cancer development and progression [19]. In addition, metformin is also a potent activator of activated protein kinase (AMPK), which in turn inhibits the mammalian target of rapamycin (mTOR) and other protein synthesis. These direct effects can lead to reduced cell proliferation [20].

A recent study has evaluated the effects of metformin on PCa focusing on the AMPK pathway in paired pre-treatment and prostatectomy specimens [21]. Although the study was limited by small sample size and lack of a control arm, a change in the proliferation marker ki67 could be observed following metformin therapy (mean 50% reduction). Together with our collaborators at the Centre for Molecular Oncologic Pathology (CMOP), Dana Farber Cancer Institute (DFCI), we have also investigated the molecular pathways involved in PCa in a cohort of 181 men. Preliminary results from the Uppsala Longitudinal Study of Adult Men (ULSAM) cohort showed that men with higher levels of fatty acid synthase (FASN) had an increased risk of prostate cancer death compared to patients with normal levels (unpublished data). Furthermore, Flavin et al. have shown that lack of AMPK activity is associated with and may be an important biochemical alteration in MetS [22].

Rationale for the study

A potential role for metformin in PCa has been suggested and given its wide availability, tolerable side effect profile and safety record it may represent a therapeutic option for men with PCa. However, the mechanism of action by which metformin exerts its anti-cancer effect has yet to be fully characterised. This 'window of opportunity' trial provides an opportunity to investigate this by comparing baseline prostate biopsies with post-treatment surgical specimen by focussing on assessment of the FASN/AMPK axis. This study will have a placebo arm in order to provide a control group. Non-diabetic patients with newly diagnosed PCa scheduled for radical prostatectomy will be eligible for treatment with metformin/placebo for four weeks prior to prostatectomy.

Risk/benefit

Usual timing between diagnostic biopsy and prostatectomy is four weeks on average, so therefore it is not expected that surgery will be delayed as a result of participation in this study. Since this is a proof of principle trial with a relative short duration of treatment, it is unlikely that patients will derive significant benefit by study participation. However, it has been shown that metformin is well tolerated in a non-diabetic population [21, 23] and it is not anticipated that patients will experience increased morbidity by study participation.

Trial design

This is a randomised, placebo-controlled, double-blind, window of opportunity study investigating the biological mechanism of metformin in PCa. Patients with newly-diagnosed, early stage, prostate cancer scheduled for radical prostatectomy will either enter the main study and be randomised 1:1 to receive metformin (2 g daily over 2 divided doses; Arm A) or placebo four weeks prior to prostatectomy (standard of care; Arm B). A subset of five patients will enter the exploratory PET-MRI sub study. These five patients will all receive metformin and will undergo an additional two PET-MRI Scans (see below).

Patients with a history of a current or historical diagnosis of diabetes mellitus and/or prior metformin use will be excluded.

The primary objective of this study is to investigate the biological mechanism of metformin on PCa using pharmacodynamic markers (Table 1). The primary endpoint for this study is the difference in expression levels of biomarkers representing the FASN/AMPK pathway for the metformin and placebo groups, as measured by the H score. Secondary endpoints include the difference in indicators of proliferation in the same groups, as well as differences in expression levels of the biomarkers between benign and malignant tissue (Table 1).

Following informed consent (see Additional file 1: Appendix 1 for informed consent form) and screening, patients in the main study will be randomised and continue metformin or placebo for four weeks until the evening prior to radical prostatectomy. The five patients in the PET-MRI sub study will all receive metformin. In the event that surgery is scheduled for after this time point, patient will continue study drug for an additional one week. Prostate tissue (at baseline from biopsy and post treatment from prostatectomy) will be used for analysis of p-AMPK, p-ACC, FASN by immunohistochemistry and proliferation will be measured using ki67 and TUNEL in both groups.

Tissue metformin levels will also be assessed in baseline and post-treatment prostate tissue in the metformin-cohort. Each tissue specimen will be assessed by an experienced uro-pathologist to identify benign and malignant tissue. Patients will also be invited to consent for tissue storage in an HTA licensed Biobank. Additional translational studies may be undertaken based upon the results of the initial analysis as described in this protocol. Study drug safety will be assessed by recording adverse events.

The primary endpoint of this study is pharmacodynamic and therefore time between study drug dose and prostatectomy is an important factor. To minimise the effects of dose reductions and interruptions, the primary endpoint analysis will be based on a per protocol analysis. Evaluable patients are defined as:

-Received at least 21 days (3 weeks) of study drug between 1.5–2.0 g daily.

-Received study drug uninterrupted for the last 7 days prior to prostatectomy.

-A secondary analysis will include an intention-to-treat analysis.

Histopathological staging from prostatectomy will be performed. Following prostatectomy, all patients will be followed up for a final safety assessment and recording

Table 1 Objectives

Objectives	Endpoints
Primary endpoints	
To determine the biological effect of metformin on markers of the FASN/AMPK pathway in prostate tissue by comparison of pre and post-treatment samples.	Assessment of the difference in expression levels of markers of the FASN/AMPK pathway pre and post treatment between the placebo and metformin arms.
Secondary endpoints	
To evaluate the biological effect of metformin on markers of proliferation in prostate tissue by comparison of pre and post-treatment samples.	Assessment of the difference in expression levels of indicators of proliferation (ki67 and Terminal deoxynudeotidyl transferase dUTP nick end labelling (TUNEL)) pre and post treatment between the placebo and metformin arms.
To evaluate differences in FASN/AMPK-associated markers in benign and malignant prostate tissue.	Assessment of the difference in expression levels of markers of the FASN/AMPK pathway and indicators of proliferation between benign and malignant prostate tissue in the placebo and metformin arms.
To measure metformin levels in prostate tissue.	Assessment of the difference in metformin levels in baseline and post-treatment prostate tissue.
To determine safety of metformin in this non-diabetic patient cohort.	Assessment of adverse events and laboratory evaluations.
To determine surgical toxicity.	Assessment of surgical-specific toxicities: time between biopsy and surgery, peri-operative bleeding, infection, rectal injury and length of hospital stay.
Exploratory Objectives and Endpoints	
To evaluate the effects of metformin on functional imaging of the prostate.	Difference in ^{18}F Choline PET/MRI between baseline and post-treatment (prior to prostatectomy) in a separate non-randomised cohort of five patients with MRI positive disease receiving metformin.

of surgical toxicity by the Clavien-Dindo system. Following this visit, patients do not require further study-related follow up and will continue to receive standard of care.

The exploratory endpoint of this study involves 18F Choline PET/MRI evaluation at baseline and post-metformin (pre-prostatectomy) for assessment of response in prostate tissue. This exploratory sub-study will include 5 patients with MRI positive disease, not randomised in the main trial, all of whom will receive metformin. Apart from the additional two visits for the 18F Choline PET/MRI scans they will follow the same trial protocol/visit schedule as those in the main study. The criteria for enrolment in to this sub study are:

1. Patient willing to undergo two additional PET-MRI scans
2. MRI positive disease
3. Satisfactory completion of MRI safety questionnaire
4. Availability of 18F Choline and scanning slots which would not result in a delay to the patient's enrolment into the study or to their surgery

Methods: Participants, interventions, and outcomes

Study setting

The trial is currently open at two tertiary referral hospitals in London, UK.

- Guy's and St Thomas NHS Foundation Trust
- Royal Marsden NHS Foundation Trust

Full details can be found on the EudraCT website https://www.clinicaltrialsregister.eu/ctr-search/search?query=2014-005193-11.

Eligibility criteria

Inclusion criteria

Patients eligible to participate in this study are those who meet all of the following inclusion criteria:

1. Age 18 or older and willing and able to provide signed informed consent.
2. Histologically confirmed adenocarcinoma of the prostate, with a maximal tumour length of greater or equal to 6 mm on core biopsy
3. No previous treatment for prostate cancer (including surgery, any hormone therapy, radiotherapy and cryotherapy)
4. Prostate biopsy within 6 months from screening
5. Radical prostatectomy is the scheduled treatment of choice
6. Eastern Cooperative Oncology Group (ECOG) Performance status less than or equal to 0 or 1
7. Adequate organ function, defined as follows:
   Haemoglobin >10.0g/dL
   Absolute neutrophil count >1.5x10^9/L
   Platelet count >100x10^9/L
   Renal function, eGFR >60ml/min (calculated by Cockcroft Gault)
   AST and/or ALT <2.5 x ULN
   Total Bilirubin <1.5 x ULN
8. Able to swallow the drug and comply with study requirements.

Exclusion criteria

Patients must NOT meet any of the following exclusion criteria:

1. Patients with a current or historical diagnosis of type one or two Diabetes and/or have ever received metformin
2. Patients with hypersensitivity to any of the components of Metformin or placebo tablet
3. History of or conditions associated with lactic acidosis such as shock or pulmonary insufficiency, alcoholism (acute or chronic), and conditions associated with hypoxaemia
4. Patients with chronic liver disease, severe cardiovascular impairment, cardiac failure, recent myocardial infarction, severe peripheral vascular disease or renal impairment (eGFR <60 ml/min as measured by Cockcroft Gault)
5. Patients with acute severe disorders, for example infections with fever, pancreatitis, trauma, dehydration or reduced diet (<1000 kcal or 4200 kJ per day)
6. Other active malignancy over the last five years that has required systemic therapy, excluding:
   a. Adjuvant therapy in the curative setting
   b. Non-melanoma skin cancer
   c. Superficial transitional cell carcinoma (CIS-T1)
7. Current enrolment in an investigational drug or device study or participation in such a study within 30 days of signing consent.
8. Any subjects who is able to father a child and does not agree to use barrier protection, in the form of a condom, for the duration of the trial and for 16 weeks after the last study drug administration.

Interventions

Screening procedures within 14 days of consent

- Written informed consent from all participants
- Clinical assessments:
  - Complete medical history, including diagnosis, history of other diseases (active or resolved), concomitant illnesses and medications.

  - Record of patient demographics
  - Physical examination including vital signs, height and weight, waist/hip ratio and ECOG performance status
- Laboratory determinations: Blood results taken within 14 days of consent for other purposes can be used as part of the screening process:Full Blood Count (FBC), renal function, liver Function Tests (LFT), bone profile, fasting glucose, PSA, testosterone, fasting lipid profile, HbA1c. Select sites will also take two additional samples for a whole blood and serum save. This will be taken according to trial specific SOP (see Additional file 2: Appendix 2).
- Radiological assessment:
  - MRI Safety Assessment
  - In subgroup of 5 patients with MRI positive disease receiving metformin: ^{18} F Choline PET/MRI
- Tissue collection: Formalin Fixed Paraffin embedded tissue will be collected from baseline diagnostic specimen.

Study week 1 (day 1):

- Clinical assessments:
  - Physical examination including ECOG performance status if greater than 7 days from screening physical examination
  - Baseline adverse events
  - Medication review
  - Given compliance diary

Study week 3 (+/− 2 days):

- Clinical assessments:
  - Physical examination, including ECOG performance status and vital signs.
  - Adverse events
  - Compliance evaluation (diary and verbal)
  - Medication revieW

- Laboratory determinations: Blood tests taken within 2 days of compliance visit for other purposes can be used as part of the compliance visit
  - FBC, renal function, LFT, bone profile

Study week 4 (+/− 1 week) pre-prostatectomy:

- Clinical assessments:
  - Physical examination, including ECOG performance status, weight, waist/hip ratio and vital signs
  - Adverse events
  - Compliance evaluation
  - Medications review
- Laboratory determinations: Blood tests taken within 2 days of surgery visit for other purposes can be used as part of the surgery visit: FBC, Renal function, LFT, bone profile, fasting glucose, PSA, testosterone, fasting lipid profile. Select sites will also take two additional samples for a whole blood and serum save. This will be taken according to trial specific SOP (see Additional file 2: Appendix 2).

- Radiological assessment: In a subgroup of 5 patients with MRI positive disease: ^{18} F Choline PET/MRI, which will be performed after 21+/− 2 days of metformin and prior to prostatectomy. A time point prior to 28 days is chosen to allow radiological assessment to be scheduled without interfering with surgery scheduling.

- A pre-operative surgical visit should occur prior to surgery, as per standard of care and local policies.

Study week 4 (+/− 1 week) – prostatectomy:

Patients will undergo prostatectomy. This will occur at the end of week 4 (+/− 1 week). Study drug treatment will continue up until the evening before surgery until the patient is nil by mouth (as per local guidelines). In the events patients undergo surgery beyond 4 weeks from randomisation; study drug will be continued for an additional 1 week. Surgery should occur as per local policies.

- If clinically necessary, surgery can be brought forward or not performed (this should be discussed with the Chief Investigator). The case should be presented to a multidisciplinary team meeting before any other non-surgical treatment is given. These patients will not be included in the analysis as, in the absence of surgery, it will not be possible to assess for post-treatment tissue markers.

- Tissue Collection: Formalin Fixed Paraffin Embedded tissue will be taken from the radical prostatectomy specimen

Follow up 8–10 weeks post operatively

- Clinical assessments:
  - Symptoms directed physical examination, including ECOG performance status, weight, waist/hip ratio and vital signs
  - Medications review
  - Adverse events and complete Clavien Dindo assessment

- Laboratory determinations: Blood tests taken within 2 days of post-operative visit for other purposes can be used as part of the post-operative visit: FBC, renal function, LFT, bone profile, PSA, testosterone.

Laboratory tests

Laboratory determinations including FBC, Renal function, LFT, bone profile, fasting glucose, PSA, testosterone, fasting lipid profile and HbA1c will be carried out by the local haematology and biochemistry laboratory at each site in accordance with local procedures.

Formalin fixed paraffin embedded tissue will be collected from baseline diagnostic biopsy and from the prostatectomy. Tissue will then be shipped to CMOP at DFCI. Samples will be processed and stored as per Laboratory Standard Operating Procedures.

The following analyses will be conducted at the CMOP on collected baseline and post-surgery tissue specimens:

- p-AMPK, p-ACC, FASN, ki-67 and TUNEL will be assessed in benign and malignant tissue by immunohistochemistry using image analysis.
- The ki-67 proliferation index is assessed by point counting 1000 cells, and is reported as percent positive cells.
- TUNEL is an apoptotic index defined as the number of apoptotic cells per 1000 tumour cells.
- Remaining markers will be measured using a H-score.

Methods for these analyses have been optimized and used in preliminary studies performed in collaboration at CMOP. Tissue (prostate) metformin concentrations will also be performed.

Radiological assessment

During screening all five men undergoing 18F Choline PET/MRI will have successfully completed a MRI standard safety questionnaire (including eGFR) and their diagnostic clinical MRI will be have been checked to ensure it has visible disease. The patient will be asked to be nil by mouth 4 h prior the the scan. The scans will consist of:

- MRI Sequences: Prostate T1 and T2-weighted images
- prostate diffusion-weighted images
- BOLD MRI and MR spectroscopy.

Dynamic contrast enhanced MRI of prostate (0.1 mmol/kg IV). PET acquisition: 350 MBq 18F–choline IV. Dynamic image acquisition over pelvis. Patients will receive IV buscopan and undergo rectal filling as per standard MRI operating procedures.

Dosing regimen

In order to limit gastrointestinal side effects patients will be instructed to take study drug at doses increasing from:

- 500 mg once a day (day 1–2)
- 500 mg twice a day (day 3–4)
- 1 g twice a day from day 5 onwards for 4 weeks until prostatectomy +/− one week

Study drug will be continued until the evening prior to surgery. Placebo will be dose escalated in the same way. Participants will be given these instructions verbally as well as written instructions at the start of their medication compliance diary.

Study drug doses should ideally be taken at the same time each day. Missed doses of the study drug may be taken later, provided that the time of dosing is at least 6 h before the next scheduled dose. If dosing is missed for one day for any reason, double-dosing should not occur the following day. Acute alcohol intoxication can increase the likelihood of the rare, but serious adverse event of lactic acidosis. Therefore, all participants will be advised to avoid alcohol for the duration of the trial. Patients participating in the non-randomised 18F PET/MRI cohort will receive metformin, which will be dose escalated as outlined above. All dose modifications and duration of treatment will be identical to the randomized cohort.

Dose reduction in case of adverse events

The investigator should determine if an adverse event is related to the study drug. Adverse events (AE) considered at least possibly related to study drug may require a dose reduction, a temporary hold (up to 7 days), or permanent discontinuation. Dose modifications should be based on the NCI CTCAE (version 4). Dose reduction for Grade 1 AEs is not required. Dose reduction for Grade 2 events should be considered only when the AE is judged by the investigator to be clinically intolerable. For Grade 3 and 4 AEs, the dose modification of study drug should follow the Dose Reduction Guidelines in the Tables 2 and 3

Table 2 General dose reduction guidelines

Grade I	Continue study treatment at same dose; monitor and treat as clinically indicated.
Grade II	Continue study treatment at same dose; monitor and treat as clinically indicated.
Grade III	Step 1. Interrupt study drug until toxicity reduced to ≤Grade 1. Step 2. Restart study treatment at same dose or lower dose at discretion of investigator
Grade IV	Step 1. Interrupt study drug until toxicity reduced to ≤Grade 2. Step 2. Restart study treatment at lower dose level.

Table 3 Dose level dose

Dose level	Dose
0	1 g BD.
-1	500 mg BD
-2	Discontinuation

below. Dose modification for Grade 3 or 4 diarrhoea should follow the guidelines in Table 4 below.

IMP risks

As Metformin is a licensed drug the reference document will be the Medley Pharma laboratories Summary of Product Characteristics (SmPC). The very common unwanted effects (less than or equal to 1 in 10) are gastrointestinal symptoms such as nausea, vomiting, diarrhoea, abdominal pain and loss of appetite.

Lactic acidosis is a rare, but serious, metabolic complication that can occur due to metformin accumulation. Reported cases of lactic acidosis in patients on metformin have occurred primarily in diabetic patients with significant renal failure. The incidence of lactic acidosis can and should be reduced by assessing other associated risk factors such as poorly controlled diabetes, ketosis, prolonged fasting, excessive alcohol intake, hepatic insufficiency and any condition associated with hypoxia. For full details please refer to the SmPC.

Drug accountability

The pharmacy will keep accountability records for reconciliation purposes. These should be used to record the identification of the subject to whom the investigational product was dispensed, the date, batch number, expiry date and quantity of the investigational product dispensed and the quantity of the investigational product unused/returned by the subject. Participants will be asked to return all packaging to pharmacy for accountability. Any excess or unused drug will be collected by the trial team, retained for verification by the local Clinical Research Associate (CRA) and destroyed by Guy's Hospital Pharmacy in accordance with local requirements when authorised to do so. Disposal of unused investigational medicinal product (IMP) is only permitted with sponsor authorisation.

Table 4 Dose reduction for specific toxicity: diarrhoea

Grade I	No action required.
Grade II	Concomitant anti-diarrhoeal agents may initially be administered without dose reduction. If Grade 2 diarrhoea persists, dose reduction should occur as per Table 2. Supportive care regimen should follow local standard of care.
Grade III	Dose reduction should occur as per Table 2.
Grade IV	Dose reduction should occur as per Table 2.

Storage of IMP

This IMP does not require any special storage conditions. IMP should be handled and stored safely and properly in accordance with the drug label. Patients will be instructed to store study drug at room temperature out of reach of children.

Subject compliance

Trial subjects will undergo a compliance evaluation at their Study week 3 (+/− 2 days) visit. This will consist of reviewing a medication diary given at enrolment and a verbal questioning about drug compliance.

Concomitant medication

For management of concomitant therapies, please refer to the SMPC.

Participant timeline

Please see below Fig. 1 for the trial schema and Table 5 for the trial flow chart.

Sample size

The primary analysis for this study will quantify the difference in expression levels of biomarkers representing the FASN/AMPK pathway, as well as indicators of proliferation, for the metformin and placebo groups as measured by the H score using a simple two-sample t-test. Secondary analyses will include a comparison of differences in expression levels of biomarkers of the FASN/AMPK pathway, as well as indicators of proliferation, between benign and malignant tissue. Finally, we will perform a multivariate regression analysis to predict effects of metformin on expression levels using tumour and patient-specific characteristics.

Our original sample size calculation was based on the H-score used to assess expression levels of the studied biomarkers, which ranges from 0 to 300. We conducted a two-sided test (alpha = 0.05; power = 0.80) comparing the mean difference in the two groups for different scenarios as we will be testing different biomarkers. Based on these scenarios, we planned to recruit 90 patients for each arm over a period of 15 months. However, since the start of our trial we have also identified other pathways to be studied in the prostate tissue. Moreover, we will set up a stratification trial following the biological information obtained in this trial. As a result we have reviewed our sample size calculation by increasing the type I error to 20% - which will require us to only recruit 50 men in each group. As we will conduct a follow-up trial with a clinical outcome, the potential type I error can be corrected for in this second trial. At the current stage it is thus more important to reduce the probability of failing to reject the null hypothesis when it is false. Hence, we have not changed the power in our

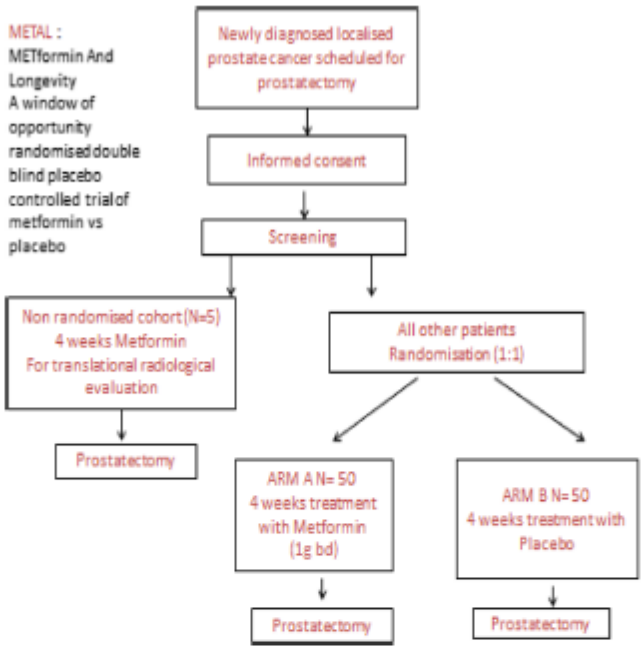

Fig. 1 Trial Schema

revised sample size calculation. Table 6 below shows the revised power calculation. In addition to the 50 patients in each arm, we will recruit an additional five patients in the exploratory endpoint group who will not be randomised.

Recruitment

Patients will be identified in multi-disciplinary team meetings or in out-patient clinics by the clinical team. Only patients with adequate diagnostic prostate biopsy specimen available for baseline immunohistochemistry will be approached for participation in this study. Assessment of this will be undertaken by an experienced uro-pathologist present during multi-disciplinary team meetings. Patients will be selected to be approached for recruitment in to either the sub study or the main study, depending on whether the criteria for the sub study are fulfilled. Patients approached about the sub study, will be able to opt for enrolment in to the main study should they wish. Once all five patients are recruited to the sub study, all subsequent patients will be approached only about the main study.

Methods: Assignment of interventions

Randomisation

Patients will be randomised using block randomisation with randomly varying block sizes. Randomisation will be performed via a web based independent randomisation service, hosted at the UKCRC registered KCTU. Researchers will access the system via http://www.ctu.co.uk and will login with individual usernames and passwords. When a patient is confirmed as eligible and consenting, their study ID, initials, and date of birth will be entered into the system, along with any relevant stratification information, and the patient will be randomised to active or placebo medication. The system will auto-generate confirmation emails to pharmacy advising of the trial arm to be dispensed. A blinded confirmation email will be generated to the rest of the research team.

Emergency code break

Investigators and patients will remain blinded to the treatment allocation throughout the trial. Unblinding should not normally be necessary as serious side-effects should be dealt with on the assumption that the patient is on active metformin treatment. Study medication should be omitted rather than unblinded. Request for unblinding should be directed to local pharmacy during office hours. In case of emergency un-blinding being necessary out of hours, the on call pharmacist should be contacted. Contact details for individual sites will be provided on site specific emergency contact list.

Table 5 Trial Flow Chart

Phase	Screening	Pre-surgery Treatment			Surgery	Post-surgery
Time point	≤14 days before baseline	Baseline Day 1 of treatment	Day 21 (+/- 2 days)	Day 28 (+/- 1 week) prior to surgery	Day 28 (+/- 1 week)	8-10[f] weeks post-op
Informed consent	x					
Eligibility review	x	x				
Randomisation		x				
Medical History[a]	x					
Demographics	x					
Physical Exam	x	x	x	x		x
Vital signs[b]	x		x	x		x
ECOG PS	x	x	x	x		x
Height	x					
Weight	x			x		x
Waist/Hip ratio	x			x		x
Haematology	x		x	x		x
Biochemistry[c]	x		x	x		x
Fasting Glucose/Lipids	x			x		
PSA and Testosterone	x			x		x
HbA1c	x					
Whole blood and Serum save[d]	X			X		
Study Drug Administration		x	x	x		
Medication review	x	x	x	x		x
Compliance evaluation (diary and verbal)			x	x		
Adverse events (CTCAE v4)[e]		x	x	x		x
Paraffin embedded tissue sent to laboratory	x				x	
Prostatectomy					x	
MRI safety assessment[g]	x					
^{18}F Choline PET/MRI[g]	x			X[e]		

[a]Full medical history, including history other disease, active or resolved, concomitant illnesses and cancer diagnosis
[b]Blood pressure, pulse rate and oxygen saturation, BM
[c]Renal profile, liver function tests, bone profile
[d]To be taken at selected sites only and according to the Trial specific SOP
[e]Clavien Dindo assessment to be completed at 8-10 weeks post operatively
[f]This review will coincide with routine post-operative review
[g]Only for the 5 subjects participating in the exploratory PET-MRI group

Withdrawal of patients

Participants have the right to withdraw from the study at any time for any reason. The investigator also has the right to withdraw patients from the study drug in the event of inter-current illness, AEs, SAE's, SUSAR's, protocol violations, administrative reasons or other reasons. It is understood by all concerned that an excessive rate of withdrawals can render the study un-interpretable; therefore, unnecessary withdrawal of patients should be avoided. Should a patient decide to withdraw from the study, all efforts will be made to report the reason for withdrawal as thoroughly as possible. Should a patient withdraw from study drug only, efforts will be made to continue to obtain follow-up data, with the permission of the patient.

Participants who wish to withdraw from IMP will be asked to confirm whether they are still willing to provide the following.

- trial specific data at their follow up visit

Patients who interrupt study drug for greater than 7 days, without the direction from their treating doctors, will be considered as non-compliant and will be discontinued from the study. These patients will be included in the safety assessments. They will be included in the pharmacodynamic, efficacy and safety assessments only if they received at least 21 days of treatment.

Table 6 Sample size calculation (two-sided test with power = 0.80) to identify mean difference in H score between biopsy and radical prostatectomy specimen for the metformin and control group

	Mean Difference (SD) in Metformin Group	Mean Difference (SD) in Control Group	N needed with α = 0.05	N needed with α = 0.10	N needed with α = 0.20
Scenario 1	15 (35)	0 (35)	86	38	50
Scenario 2	30 (65)	0 (65)	74	59	43
Scenario 3	20 (25)	5 (25)	44	35	26
Scenario 4	30 (50)	5 (50)	63	50	37

Treatment with study drug should be discontinued if it is considered to be in the best interest of the patient. Reasons for treatment discontinuation include:

- Disease progression
- Occurrence of intolerable side effects
- Patient withdrawal of consent or non-compliance.

Patients discontinued from the study for reasons unrelated to therapy, such as non-compliance, ineligibility or withdrawal of consent will be considered drop-outs. All of these patients are still evaluable for toxicity. Any subjects who withdraw prior to completing treatment will be replaced until 90 subjects in each of the randomized study arms have completed treatment.

Methods: Data collection, management and analysis

A separate data management plan will be created for the trial. The case report forms will be paper based. They will be collated and completed by the clinical trial coordinator and dedicated research nurse. A password protected database will be created on the ACCESS platform to allow speed of data entry.

The Chief Investigator will act as custodian for the trial data. The following guidelines will be strictly adhered to: Patient data will be anonymised.

- All anonymised data will be stored on a password protected encrypted computer.
- All trial data will be stored in line with the Medicines for Human Use (Clinical Trials) Amended Regulations 2006 and the Data Protection Act and archived in line with the Medicines for Human Use (Clinical Trials) Amended Regulations 2006 as defined in the Kings Health Partners Clinical Trials Office Archiving SOP.

Per protocol analysis

The primary endpoint of this study is pharmacodynamic and therefore time between study drug dose and prostatectomy is an important factor for evaluation of the primary endpoint. To minimize the effects of dose reductions and interruptions, the primary endpoint analysis will be based on a per protocol analysis. Evaluable patients are defined as:

- Received at least 21 days (3 weeks) of study drug between 1.5–2.0 g daily.
- Received study drug uninterrupted for the last 7 days prior to prostatectomy.

Intention-to-treat population

The intention-to-Treat (ITT) population is defined as all patients who were randomised in this study. The ITT population will be analysed by treatment arm as randomised (i.e. treatment arm based on randomisation assignment).

Safety analysis

The safety population is defined as all randomised patients who received at least 1 dose or partial dose of study drug. The safety population will be analysed by treatment arm as treated. The safety population will be used to conduct safety analyses.

Exploratory analysis

Exploratory analysis by ^{18}F Choline PET/MRI will be performed in five patients with MRI positive disease who will not be randomised and will all receive metformin. This patient population will be used to conduct exploratory analyses. Once five complete datasets are completed no further recruitment to this group will occur. Data will be summarised descriptively.

Accrual and duration of study

The estimated accrual for this study is 10 patients a month. Allowing for a 5% drop out rate, patient accrual is expected to be completed within 18 months. We will account for all of the patients registered in the study. The number of patients who were not evaluable, who died or withdrew before treatment began will be specified. The distribution of follow-up time will be described and the number of patients lost to follow-up will be given.

Methods: Monitoring

Neither the co-sponsors nor the investigators felt this study warranted a data monitoring committee (DMC)

given the use of metformin which is a safe, well tolerated post licensed drug.

Reporting responsibilities

Organisations have delegated the delivery of the Sponsor's responsibility for Pharmacovigilance (as defined in Regulation 5 of the Medicines for Human Use (Clinical Trials) Regulations 2004 to the King's Health Partners Clinical Trials Office (KHP-CTO).

All SAEs, SARs and SUSARs will be reported immediately by the Chief Investigator (and certainly no later than 24 h) to the KHP-CTO in accordance with the current Pharmacovigilance Policy. Death as a result of disease progression and other events that are primary or secondary outcome measures are not considered to be SAEs and should be reported in the normal way, on the appropriate CRF.

The KHP-CTO will report SUSARs to the regulatory authorities Medicines and Healthcare products Regulatory Agency (MHRA), competent authorities of other European Economic Area states in which the trial is taking place.

The Chief Investigator will report to the relevant ethics committee. Reporting timelines are as follows:

- SUSARs which are fatal or life-threatening must be reported not later than 7 days after the sponsor is first aware of the reaction. Any additional relevant information must be reported within a further 8 days.
- SUSARs that are not fatal or life-threatening must be reported within 15 days of the sponsor first becoming aware of the reaction.

The Chief Investigator and KHP-CTO (on behalf of the *co*-sponsors) will submit a Development Safety Update Report (DSUR) relating to this trial IMP to the MHRA and REC annually. Monitoring of this trial will be to ensure compliance with Good Clinical Practice and scientific integrity will be managed and oversight retained, by the KHP-CTO Quality Team.

Ethics and dissemination

The trial will be conducted in compliance with the principles of the Declaration of Helsinki (1996), the principles of GCP and in accordance with all applicable regulatory requirements including but not limited to the Research Governance Framework and the Medicines for Human Use (Clinical Trial) Regulations 2004, as amended in 2006 and any subsequent amendments.

This protocol and related documents have been submitted for review to Fulham Research Ethics Committee (REC), and to the MHRA for Clinical Trial Authorisation, as will all substantial and non-substantial amendments. The Chief Investigator will submit a final report at conclusion of the trial to the KHP-CTO (on behalf of the Sponsor), the REC and the MHRA within the timelines defined in the Regulations.

The co-sponsors, King's College London and Guy's and St Thomas NHS Foundation Trust, will provide insurance and indemnity. Funding to conduct the trial is provided kindly by the JP Moulton Charitable Foundation. It is intended that the results of the study will be reported and disseminated at international conferences and in peer-reviewed scientific journals.

Discussion

This multi-site randomised placebo-controlled double blinded trial of metformin vs. placebo in men with localised prostate cancer due to undergo radical prostatectomy aims to elucidate the mechanism of action of metformin in PCa cells, which should then enable further larger stratification trials using metformin in different stages of PCa to take place.

Additional files

Additional file 1: Appendix 1. Informed Consent Form. (DOC 213 kb)
Additional file 2: Appendix 2. SOP serum and whole blood preperation. (DOCX 23.8 kb)

Abbreviations

AE: Adverse event; AMPK: Activated protein kinase; CMOP: Centre for Molecular Oncologic Pathology (CMOP); CRA: Clinical research associate; DFCI: Dana Farber Cancer Institute (DFCI); DMC: Data monitoring committee; FASN: Fatty acid synthase; FBC: Full blood count; IGF-1: Insulin like growth factor – 1; IMP: Investigational medicinal product; ITT: Intention to treat; KCTU: King's College clinical trial unit; LFTs: Liver function tests; METAL: Metformin and longevity; MetS: Metabolic syndrome; MHRA: Medicines and Healthcare products Regulatory Agency; MTOR: Mammalian target of rapamycin; NCI CTCAE: National cancer institute common terminology criteria for adverse events; PCa: Prostate cancer; PSA: Prostate specific antigen; REC: Research ethics committee; SAE: Serious adverse event; SAR: Serious adverse reaction; SMPC: Summary of product characteristics; SOP: Standard operating procedure; SUSAR: Suspected unexpected serious Adverse Reaction; T2DM: Type two diabetes mellitus; TUNEL: Terminal deoxynucleotidyl transferase dUTP nick end labelling; ULSAM: Uppsala Longitudinal Study of Adult Men

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Funding

Funding to conduct the trial is provided kindly by the JP Moulton Charitable Foundation. The funders have no role in the design, management or presentation of the trial.

Availability of data and materials

Not applicable.

Authors' contributions
D Crawley- contributed to conception and trial design, wrote protocol, trial coordinator and co-investigator. AC- contributed to conception and trial design. ML- contributed to conception and trial design. CG- contributed to conception and trial design. PC- Co-investigator on trial. BC- contributed to conception and trial design and Co-investigator on trial. GC- contributed to conception and trial design. D Cahill- contributed to conception and trial design and is Chief Investigator at RMH. AO- contributed to conception and trial design. FC- contributed to conception and trial design. GG- contributed to conception and trial design. SR- contributed to conception and trial design and trial Principle Investigator. MH- contributed to conception and trial design and trial statistician. All authors read and approved the final manuscript.

Ethics approval and consent to participate
Ethical approval has been granted for this study by the Fulham NRES Committee. Reference: 15 LO 0290. All patients must give written informed consent to participate. EudraCT number 2014–005193-11. Registered on 09/02/2015.

Consent for publication
Not applicable.

Competing interests
The authors declare that they have no competing interests.

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SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Metformin 500mg Tablets BP

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

1 film-coated tablet contains metformin hydrochloride 500 mg

For excipients see 6.1

3 PHARMACEUTICAL FORM

Film-coated tablets

White coloured, film-coated, round, biconvex tablets

OR

White coloured, film-coated, round, biconvex tablets embossed 'M500' on one side and plain on the other side.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

- Non-insulin-dependent diabetes (NIDDM, type II) and, in particular, in obese patients, when adequate dietary treatment has failed.

- Metformin 500mg Tablets BP can be given alone as initial therapy, or can be administered in combination with sulphonylureas after careful assessment of the contra-indications.

4.2 Posology and method of administration

Dosage

Usual dosage:

The required daily dose ranges from 0.5 to 3 g . The usual starting dose is one 500mg tablet three times a day or one 850mg tablet twice a day. The daily dose should be divided and taken with or after meals in order to minimise the gastro-intestinal side effects. If diabetic control is incomplete a cautious increase in dosage to a maximum of 3g daily is justified. No additional benefit can usually be achieved by use of doses exceeding 3 g daily. Once control has been achieved it may be possible to reduce the daily dose.

In cases of metabolic decompensation:

The metformin hydrochloride dosage may be reduced in cases of metabolic decompensation. If only small daily doses are administered an omission of one metformin hydrochloride dose should be tried. This is of importance in elderly patients to reduce the risk of lactic acidosis.

Children and juveniles:

Metformin 500mg Tablets BP are not recommended for use in children.

Elderly patients:

Metformin 500mg Tablets BP are indicated for use in the elderly.

Further dosage information

Combination with sulphonylureas:

Metformin 500mg Tablets BP may be used in combination with sulphonylureas if monotherapy with metformin hydrochloride does not lead to a satisfactory response. However, it should be noted that metformin hydrochloride and sulphonylureas have a different mode of action and therefore an additive or potentiating effect of these drugs might cause a hypoglycaemic shock.

Substitution for sulphonylureas:

Metformin 500mg Tablets BP may be used instead of sulphonylureas in patients who formerly have been treated with sulphonylureas.

Method of administration

Metformin 500mg Tablets BP should be taken whole with a glass of water during or after meals. They should not be chewed.

Monitoring advice

See special warnings and special precautions for use.

4.3 Contraindications

- In patients with non-insulin-dependent diabetes (NIDDM, type II), if sulphonylurea therapy has completely failed
- Diabetic precoma, coma and ketoacidosis
- Hypersensitivity to metformin hydrochloride
- Impaired renal function of any degree
- Chronic liver disease
- Severe cardiovascular impairment.
- Cardiac failure and recent myocardial infarction.
- Severe peripheral vascular disease
- Acute severe disorders, for example infections with fever, pancreatitis or trauma
- Dehydration
- History of or conditions associated with lactic acidosis such as shock or pulmonary insufficiency, alcoholism (acute or chronic), and conditions associated with hypoxaemia
- Reduced diet (< 1000 kcal or 4200 kJ per day)
- Pregnancy.

4.4 Special warnings and precautions for use

- In patients with impaired liver function, lactate clearance may be restricted.
- The risks of lactic acidosis and accumulation are determined by renal function. Therefore, metformin hydrochloride therapy requires a normal renal function which should be monitored continuously, particularly in the elderly.
- In elderly patients (approximately over the age of 65 years) metabolism is reduced and therefore a risk/benefit assessment should be carried out.
- During concomitant therapy with sulphonylureas or insulin, blood glucose levels should be monitored because combined therapy may cause hypoglycaemia. Stabilisation of diabetic patients with metformin hydrochloride and insulin should be carried out in a hospital until the correct ratio of the two drugs has been obtained.
- Metformin hydrochloride therapy should be stopped before, during and after surgery under general anaesthesia.
- Intravascular contrast studies with iodinated materials can lead to acute alteration of renal function and have been associated with lactic acidosis in patients receiving metformin. Therefore, in patients in whom any such studies are planned, metformin hydrochloride should be discontinued at the time of, or prior to, the procedure and withheld for 48 hours subsequent to the procedure and re-instituted only after renal function has been re-evaluated and found to be normal.
- Patients receiving continuous metformin hydrochloride therapy should have an annual estimation of Vitamin B_{12} levels because of reports of decreased Vitamin B_{12} absorption.

Precautions for use

- Patients should be warned to consult a physician immediately if they suddenly suffer from muscle spasms, dyspepsia, abdominal pain and fatigue, since these symptoms may indicate lactic acidosis. Lactic acidosis is accompanied by acidotic dyspnoea, abdominal pain, hyperthermia, comatose state, decrease of blood pH value and increase of lactate value.
- Serum creatinine levels should be determined before and four weeks after metformin hydrochloride therapy has been started. Regular measurements should take place once or twice a year unless required earlier due to intercurrent disorders. In elderly patients serum creatinine values often are not meaningful. Therefore, creatinine clearance should be tested before the onset of metformin hydrochloride therapy.

4.5 Interaction with other medicinal products and other forms of interaction

Contra-indicated

During treatment with Metformin 500mg Tablets BP alcohol should be strictly avoided. Alcohol may enhance the hypoglycaemic effect and produce an increased risk of lactic acidosis.

Precaution for use

An increase of the antihyperglycaemic effect of metformin hydrochloride is possible in the event of concomitant administration with medicinal products for the same indication, for example:

- Insulin
- Oral antidiabetic drugs, of the sulphonylurea and acarbose type

An increase of the antihyperglycaemic effect of metformin hydrochloride is also possible in the event of concomitant administration with medicinal products for other indications which possess blood glucose-lowering effects of their own, for example:

- NSAIDs, e.g. salicylates or pyrazolones
- MAO inhibitors
- Oxytetracycline
- ACE inhibitors
- Clofibrate derivatives
- Cyclophosphamide and its derivatives

⇨ The combination of metformin and the above mentioned drugs can induce hypoglycaemia.

Moreover, during permanent therapy, beta-blockers and antisympathotonic drugs, such as clonidine, reserpine or guanethidine, may decrease blood glucose levels. However, of particular clinical relevance is their reducing action on the hormonal and neural counterregulation during hyperglycaemia, which in turn also impairs the subjective perception of hypoglycaemic warning signs.

A decrease of the antihyperglycaemic effect of metformin hydrochloride in combination with one of the following drugs may occur:

- Glucocorticoids
- Oestrogen-Progestagen-Combinations
- Adrenaline and other Sympathomimetics
- Glucagon
- Thyroid hormones
- Thiazides and loop diuretics
- Diazoxide
- Phenothiazines
- Nicotinic acid derivatives

Guar:	A decrease of the absorption of metformin hydrochloride may lead to an attenuation of metformin effects.
Cimetidine:	Substances which delay the elimination of metformin hydrochloride, e.g. cimetidine, may increase the risk of lactic acidosis.
Phenprocoumone:	Elimination of phenprocoumone and other coumarins may be accelerated during metformin hydrochloride therapy. Therefore the blood coagulation inhibiting effect may be decreased and frequent controls of blood coagulation are necessary.

To be taken into account

During maintenance therapy the onset or termination of any other additional therapy can disturb the control of diabetes.

4.6 Fertility, Pregnancy and lactation

Pregnancy

During pregnancy the administration of Metformin 500mg Tablets BP is contra-indicated. Diabetes mellitus should be treated with insulin during pregnancy or when pregnancy is desired. Animal studies have shown no particular effects with respect to reproduction and fertility. In man insufficient experience with metformin hydrochloride during pregnancy has been obtained.

Use during lactation

The use of Metformin 500mg Tablets BP should be avoided in women who are breast-feeding. No information is available on whether metformin hydrochloride or its metabolites are excreted in the breast milk.

4.7 Effects on ability to drive and use machines

When used as monotherapy metformin hydrochloride does not influence the ability to drive or operate machinery. In cases of combined therapy with sulphonylureas or other drugs with blood glucose lowering effects, hypoglycaemia may occur and, hence, such combinations may produce minor or moderate adverse effects. Patients undergoing such combination therapy should be warned about the possible adverse effects of hypoglycaemia.

4.8 Undesirable effects

Frequently arising undesirable effects are: Gastro-intestinal disturbances

- Metformin 500mg Tablets BP are normally well tolerated, but at the beginning of metformin hydrochloride therapy gastro-intestinal disturbances, such as nausea, vomiting, abdominal pain, diarrhoea, anorexia and metallic taste occur in 5 - 20% of patients. These gastro-intestinal disturbances are generally of minor importance and require no termination of metformin hydrochloride therapy. The frequency and severity of these gastro-intestinal disturbances can be reduced markedly by starting with low and gradually increasing metformin hydrochloride doses and by administration of metformin with or after meals.
- About 5 % of all patients do not tolerate metformin hydrochloride therapy.

Very rarely arising undesirable effects are: Hypersensitivity and lactic acidosis

- Hypersensitivity reactions of the skin.
- Lactic acidosis.

Under metformin hydrochloride therapy lactic acidosis with coma and death is possible. Lactic acidosis induced by metformin hydrochloride is an indicator for a general cell toxicity and is accompanied by impaired hepatic lactate clearance and increased muscular lactate release. Although metformin hydrochloride-induced lactic acidosis occurs very rarely the lethality reaches 50 %.

Causes of lactic acidosis: Apart from overdosage other causes of lactic acidosis may be renal insufficiency, impaired liver function, alcohol consumption, other diseases with effects on oxidative metabolism, for example cardiac decompensation or severe infections and catabolic conditions as well as interactions with other drugs.

Symptoms of lactic acidosis: At first lactic acidosis resembles the gastro-intestinal side-effects of metformin hydrochloride, for example nausea, vomiting, diarrhoea and abdominal pain. However, within a few hours the complete clinical picture of lactic acidosis with muscle pains, hyperventilation, clouding of consciousness and coma may develop. On suspicion of lactic acidosis metformin therapy must be immediately stopped and the patient must be treated at once as an emergency in hospital

Reported single cases:

- Inhibition of the absorption of Vitamin B_{12} or folic acid may cause megaloblastic

anaemia. Therefore, patients receiving continuous metformin hydrochloride therapy should have an annual estimation of Vitamin B_{12} levels and, if necessary, Vitamin B_{12} has to be given parenterally.
- Persisting gastro-intestinal disturbances require the termination of metformin hydrochloride therapy.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the Yellow Card Scheme, website www.mhra.gov.uk/yellowcard.

4.9 Overdose

Human experience

Intoxication with metformin hydrochloride does not lead to hypoglycaemia but lactic acidosis may develop. Hypoglycaemia can occur when metformin hydrochloride is given concomitantly with sulphonylureas, alcohol or insulin.

Management of overdosage in man

In cases of metformin hydrochloride overdosage, for example in attempted suicide, or if signs of lactic acidosis are shown, patients must be admitted to a hospital as an emergency. The diagnosis of lactic acidosis should be confirmed by determination of lactate and metformin hydrochloride concentrations. Haemodialysis is the most effective measure to eliminate lactate and metformin. Symptomatic treatment includes circulatory stabilisation, compensation of acidosis and elimination of hypoxia. The metformin hydrochloride concentration in erythrocytes is a good indicator for accumulation and can be used to decide whether repeated haemodialysis is indicated.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Metformin hydrochloride is a biguanide oral antihyperglycaemic agent (ATC Code A10B A02) and reduces elevated blood glucose levels only in patients with non-insulin-dependent diabetes (NIDDM), but does not increase insulin secretion and does not cause hypoglycaemia or increased weight gain. Its mode of action is multifactorial and not yet completely understood. However, the augmentation of glucose uptake into peripheral tissues may influence glucose utilisation. Furthermore, the effects of metformin hydrochloride include reduced hepatic gluconeogenesis and delayed intestinal glucose absorption which may explain the blood glucose-lowering effect. The efficacy of metformin hydrochloride is dependent on a minimum concentration of

insulin. A slight influence of the insulin secretion by metformin hydrochloride is possible but a clinical relevance is not very likely. Metformin hydrochloride seems to potentiate insulin action by enhancing insulin binding to its receptors and by facilitating steps in the post-receptor pathways of insulin-action. Apart from the glucose-lowering effect, metformin hydrochloride reduces the serum triglyceride level and possesses antithrombotic properties.

5.2 Pharmacokinetic properties

After oral administration metformin hydrochloride is incompletely absorbed from the gastro-intestinal tract. The oral bioavailability of usual doses is 50 - 60 %. The maximum plasma concentration is achieved after about 2 hours. Gastrointestinal absorption is complete within 6 hours of ingestion. The volume of distribution lies between 63 and 276 litres. Metformin hydrochloride is rapidly distributed but a slow transfer to a deep compartment seems to occur. Metformin hydrochloride does not bind to plasma proteins but accumulates in the salivary glands, duodenum, kidneys and liver. No metabolites or conjugates of metformin hydrochloride have been identified. Metformin hydrochloride is completely eliminated by renal excretion and the mean plasma elimination half-life ranges between 1.5 and 4.5 hours. A quantitatively minor terminal elimination phase, probably out of the deep compartment, with a longer mean half-life ranging from 8.9 to 19 hours, has been observed. The renal clearance of metformin hydrochloride ranges between 350 and 550 ml/min and correlates with the creatinine clearance, indicating that metformin hydrochloride is excreted by active tubular secretion. In patients with impaired renal function accumulation of metformin hydrochloride is probable.

5.3 Preclinical safety data

Acute toxicity:

Acute toxicity after different routes of administration and in different animals was investigated. The data indicate the highest toxicity of metformin hydrochloride after subcutaneous administration to guinea pigs and rabbits (LD_{50} = 150 mg/kg) and intravenous administration to mice (LD_{50} = 180 mg/kg). The toxicity after oral ingestion of metformin hydrochloride seems to be several times lower, rabbits and guinea pigs (LD_{50} 350 and 500 mg/kg, respectively) being more sensitive than mice or rats (LD_{50} 1450 mg/kg and 1000 mg, respectively). Hence, in various animal species studied, after different routes of administration the LD_{50} values are considerably higher than the therapeutic dose range in humans (maximum approximately 40 mg/kg/day). The data indicate a low potential of acute toxicity.

Chronic toxicity:

Studies with repeated administration of metformin hydrochloride to rats (up to 18 months), dogs (up to 18 months) and monkeys (up to 2 years) revealed no specific toxic effects.

Mutagenic and carcinogenic effects:

Bacterial tests for mutagenicity of metformin hydrochloride were negative but chromosomal alterations were observed *in vitro* in mammalian cells. The relevance of these effects remains obscure. Long-term animal studies failed to detect any oncogenic properties of metformin hydrochloride.

Reproductive toxicity:

No teratogenic properties of metformin hydrochloride have been found in rats. The no adverse-effect level (NOAEL) of metformin in rats was estimated to be 300 mg/kg/day for embryotoxicity and female reproduction and up to 600 mg/kg/day for male fertility. No teratogenic effects were observed in rabbits with doses up to 140 mg/kg/day (p.o.). In rats doses up to 600 mg/kg/day administered p.o. pre- and postnatally showed no effects.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Core

- Sodium starch glycollate
- Maize starch
- Povidone
- Colloidal anhydrous silica
- Magnesium stearate

Film-coating

- Hypromellose
- Titanium dioxide E171
- Propylene glycol
- Macrogol 6000
- Purified talc

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

3 years

6.4 Special precautions for storage

Do not store above 25°C.

6.5 Nature and contents of container

PVC/Aluminium blister packs in outer cardboard cartons.
Contents: 28 or 84 film-coated tablets.

Securitainer (LDPE) with tamper-proof closures (HDPE) containing 500 tablets. A desiccant is included in the pack.

6.6 Special precautions for disposal

No special precautions are required.

7 MARKETING AUTHORISATION HOLDER

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